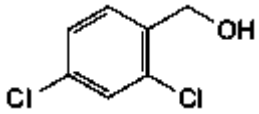
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

2,4-Dichlorobenzyl Alcohol

General Notices

(Ph. Eur. monograph 2410)



$C_7H_6Cl_2O$ 177.0 *1777-82-8*

Ph Eur

DEFINITION

(2,4-Dichlorophenyl)methanol.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, very soluble in ethanol (96 per cent).

mp

About 59 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *2,4-dichlorobenzyl alcohol CRS*.

TESTS

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, water R (50:50 *V/V*).

Buffer solution Dissolve 0.68 g of potassium dihydrogen phosphate R in 900 mL of water R, adjust to pH 3.0 with phosphoric acid R and dilute to 1000.0 mL with water R.

Test solution (a) Dissolve 0.100 g of the substance to be examined in 10.0 mL of acetonitrile R1 and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 20.0 mg of 2,4-dichlorobenzyl alcohol impurity A CRS and 20.0 mg of 2,4-dichlorobenzyl alcohol impurity C CRS in 100.0 mL of acetonitrile R1. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 0.100 g of 2,4-dichlorobenzyl alcohol CRS in 10.0 mL of acetonitrile R1 and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: methanol R2, acetonitrile R1, buffer solution (20:30:50 *V/V/V*);

— *mobile phase B*: acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	100	0
7 - 17	100 → 20	0 → 80
17 - 30	20	80

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to 2,4-dichlorobenzyl alcohol (retention time = about 7 min): impurity C = about 0.87; impurity A = about 0.91.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of 2,4-dichlorobenzyl alcohol in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

Maximum 0.2 per cent, determined on 0.500 g using the evaporation technique:

— *temperature*: 120 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

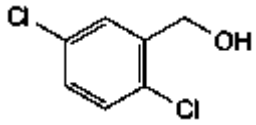
Calculate the percentage content of $C_7H_6Cl_2O$ taking into account the assigned content of *2,4-dichlorobenzyl alcohol CRS*.

IMPURITIES

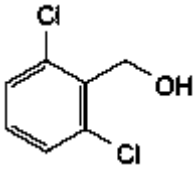
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G.*

www.webofpharma.com

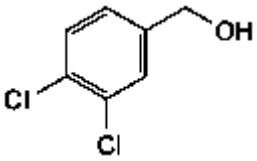
https://thuocngocanh.com/



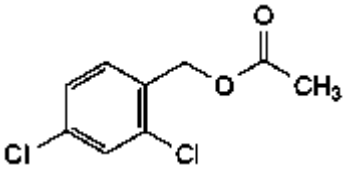
A. (2,5-dichlorophenyl)methanol,



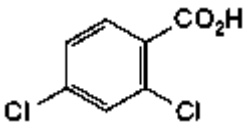
B. (2,6-dichlorophenyl)methanol,



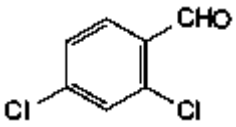
C. (3,4-dichlorophenyl)methanol,



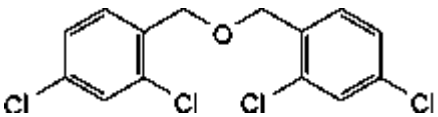
D. 2,4-dichlorobenzyl acetate,



E. 2,4-dichlorobenzoic acid,



F. 2,4-dichlorobenzaldehyde,



G. 1,1'-(oxydimethylene)bis(2,4-dichlorobenzene).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

3-*O*-Desacyl-4′-Monophosphoryl Lipid A

General Notices

(Ph. Eur. monograph 2537)

Ph Eur

DEFINITION

3-*O*-Desacyl-4′-monophosphoryl lipid A is a detoxified derivative of the lipopolysaccharide (LPS) of *Salmonella minnesota*, strain R595, which retains the immunostimulatory activities of the parent LPS. It consists of a mixture of congeners, all containing a backbone of β1′→6-linked disaccharide of 2-deoxy-2-aminoglucose phosphorylated at the 4′-position, but differing in the fatty acid substitutions at the 2, 2′ and 3′ positions. The immunostimulatory activities of 3-*O*-desacyl-4′-monophosphoryl lipid A combined with the vaccine include up-regulation of co-stimulatory molecules on antigen-presenting cells and secretion of pro-inflammatory cytokines, resulting in an enhanced immune response of the Th1-type against the antigens. 3-*O*-desacyl-4′-monophosphoryl lipid A is a lyophilised powder or a sterile liquid.

Requirements given in the sections up to and including the section Triethylamine salt of 3-*O*-desacyl-4′-monophosphoryl lipid A also apply to formulations that do not proceed to the 3-*O*-desacyl-4′-monophosphoryl lipid A liquid bulk.

PRODUCTION

GENERAL PROVISIONS

The production method shall have been shown to yield consistently a 3-*O*-desacyl-4′-monophosphoryl lipid A comparable in structure and function with a preparation of 3-*O*-desacyl-4′-monophosphoryl lipid A used as adjuvant in the particular vaccine of proven clinical efficacy and safety in man.

During development studies, and wherever revalidation is necessary, a test for residual endotoxin activity is carried out by injecting intravenously 12-day-old embryonated hens' eggs with 0.1 mL of dilutions of the test sample (8 eggs per dilution) of 3-*O*-desacyl-4′-monophosphoryl lipid A. Eggs are candled and read for mortality at 18-24 hours post-inoculation and the chick embryo 50 per cent lethal dose ($CELD_{50}$) is calculated. The residual endotoxin activity of the 3-*O*-desacyl-4′-monophosphoryl lipid A is acceptable if the $CELD_{50}$ is more than 100 µg.

An endotoxin standard of *Salmonella typhimurium* is prepared and selected dilutions are injected into each group of 8 eggs.

For a test to be valid, the $CELD_{50}$ of the endotoxin standard must not be more than 0.05 µg.

Reference preparation A batch of 3-*O*-desacyl-4′-monophosphoryl lipid A shown to be comparable in structure and function with a preparation of 3-*O*-desacyl-4′-monophosphoryl lipid A used as adjuvant in the particular vaccine of proven clinical efficacy and safety in man or a batch representative thereof.

www.webofpharma.com

https://nhathuocngocanh.com/

BACTERIAL SEED LOTS

The bacterial strain used for master seed lots shall be identified by historical records that include information on its origin and the tests used to characterise the strain, in particular genotypic and phenotypic information. Only a working seed lot that complies with the following requirements may be used.

Identification

The working seed lot is identified by suitable methods such as Gram staining and fatty acid profiling (5.1.6).

Microbial Purity

Each seed lot complies with the requirements for absence of contaminating organisms. Purity of bacterial cultures is verified by methods of suitable sensitivity and specificity.

PROPAGATION AND HARVEST

The bacteria is grown using a suitable liquid medium. At the end of cultivation, the culture is tested for purity and yield. The culture medium is separated from the bacterial mass by a suitable method, for example filtration. Only a harvest that is consistent with respect to the profiles for growth rate, pH, and O_2-consumption may be used for the extraction of LPS.

TRIETHYLAMINE SALT OF 3-O-DESACYL-4'-MONOPHOSPHORYL LIPID A

LPS is extracted from the bacterial cells by successive alcohol and chloroform-methanol extractions and is then converted to 3-*O*-desacyl-4′-monophosphoryl lipid A by hydrolysis, then purified and salified by triethanolamine before freeze-drying. The freeze-dried triethylamine salt of 3-*O*-desacyl-4′-monophosphoryl lipid A must comply with the following requirements.

Appearance

A visual description of the particular preparation after freeze-drying is established and approved by the competent authority; each batch of freeze-dried triethylamine salt of 3-*O*-desacyl-4′-monophosphoryl lipid A must comply with this description.

Protein

Less than 0.5 per cent *m/m*, determined using a suitable method, for example a reversed-phase HPLC method for amino acid analysis (2.2.56). The total amino acid content in micrograms is calculated by comparison to amino acid standards and is equal to the protein concentration.

Nucleic acid

Maximum 0.3 per cent *m/m*, determined using a suitable method. For example, a fluorimetric method may be used where nucleic acids are extracted from the freeze-dried triethylamine salt of 3-*O*-desacyl-4′-monophosphoryl lipid A, using a solution containing NH_4OH and a suitable non-ionic detergent, and stained by a suitable fluorescent dye. The nucleic acid content in the test sample is interpolated from a calibration curve.

www.webofpharma.com

https://thuocngocanh.com/

Hexosamine (2.5.20)

1000 nmol/mg to 1450 nmol/mg.

Phosphorus (2.5.18)

0.5 µmol/mg to 0.8 µmol/mg.

Congener distribution

The relative amount of tetraacyl, pentaacyl, hexaacyl and heptaacyl congener groups are determined by a suitable method, for example reversed-phase HPLC analysis (2.2.29).

The relative amount of each congener group in the triethylamine salt of 3-*O*-desacyl-4′-monophosphoryl lipid A is:

— tetraacyl: 15 per cent to 35 per cent;

— pentaacyl: 35 per cent to 60 per cent;

— hexaacyl: 20 per cent to 40 per cent;

— heptaacyl: less than 0.5 per cent.

Triethylamine

4.2 to 5.8 per cent *m/m*, determined by a suitable method, for example gas chromatography (2.2.28).

Water (2.5.12)

Maximum 6.7 per cent *m/m*.

Free fatty acids

Maximum 2.6 per cent *m/m*, determined by a suitable method, for example reversed-phase HPLC analysis (2.2.29).

2-Keto-3-deoxyoctonate

Less than 0.5 per cent *m/m*, determined by a suitable method. For example, a colorimetric method may be used where 2-keto-3-deoxyoctonate is released by hydrolysis (0.2 N H_2SO_4 at 100 °C for 30 min), oxidised by periodic acid, and reacted with sodium arsenite to yield β-formylpyruvic acid, which subsequently is coupled to thiobarbituric acid to give a red coloured chromophore with absorption maximum at 550 nm. The amount of 2-keto-3-deoxyoctonate is interpolated from a calibration curve.

Identity

The test for congener distribution also serves to identify the product.

Microbial contamination

TAMC: acceptance criterion 10^1 CFU/10 mg (2.6.12).

www.webofpharma.com

https://thuocngocanh.com/

Pyrogens (*2.6.8*)

The triethylamine salt of 3-*O*-desacyl-4′-monophosphoryl lipid A complies with the test for pyrogens. Inject into each rabbit per kilogram of body mass 3 mL of a solution containing 2.5 µg of 3-*O*-desacyl-4′-monophosphoryl lipid A.

3-O-DESACYL-4'-MONOPHOSPHORYL LIPID A LIQUID BULK

The triethylamine salt of 3-*O*-desacyl-4′-monophosphoryl lipid A is dispersed in a liquid suitable for the subsequent processing steps at a defined target concentration. If the salt is not soluble in water a microfluidisation step is necessary to prepare a stable aqueous suspension.

The liquid bulk is sterilised by filtration through a bacteria-retentive filter.

Only a 3-*O*-desacyl-4′-monophosphoryl lipid A liquid bulk that complies with the requirements given below under Identification, Tests and Assay and that is within the limits approved for the particular product may be used for the preparation of 3-*O*-desacyl-4′-monophosphoryl lipid A in the final lots.

CHARACTERS

When dispersed in an aqueous solution: slightly turbid suspension.

When dissolved in an organic solvent: a description of its appearance is established and approved by the competent authority; the 3-*O*-desacyl-4′-monophosphoryl lipid A liquid bulk complies with this description.

IDENTIFICATION

Congener distribution (see Tests).

TESTS

Particle size

Where applicable, the particle size in the microfluidised liquid bulk is determined by a suitable method, for example dynamic light scattering. The particle size for each batch of liquid bulk is within the limits approved for the particular product.

Sterility (*2.6.1*)

It complies with the test, carried out using 10 mL for each medium.

Congener distribution

The relative amount of tetraacyl, pentaacyl, hexaacyl and heptaacyl congener groups are determined by a suitable method, for example reversed-phase HPLC analysis (*2.2.29*).

The relative amount of each congener group in the 3-*O*-desacyl-4′-monophosphoryl lipid A liquid bulk is:

— tetraacyl: 15 per cent to 35 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— pentaacyl: 35 per cent to 60 per cent;

— hexaacyl: 20 per cent to 40 per cent;

— heptaacyl: less than 0.5 per cent.

ASSAY

The 3-*O*-desacyl-4′-monophosphoryl lipid A content is determined by a suitable method, for example gas chromatographic quantification (*2.2.28*) of trifluoroacetic anhydride derivatised fatty acid methyl esters of the 3-*O*-desacyl-4′-monophosphoryl lipid A fatty acids dodecanoic acid (C12:0), tetradecanoic acid (C14:0), 3-hydroxy tetradecanoic acid (3-OH-C14:0) and hexadecanoic acid (C16:0) obtained by hydrolysis of 3-*O*-desacyl-4′-monophosphoryl lipid A in an aqueous/methanol (50:50 *V/V*) solution, containing 5 per cent of sodium hydroxide. To the test sample, a reference sample and the dilutions of the calibration curve, pentadecanoic acid (C15:0) is added as an internal standard. The temperature gradient applied must allow the separation of the fatty acid methyl esters in about 40 min.

The sum of the ratios between the area for each individual fatty acid methyl ester (C12:0, C14:0, 3-OH-C14:0 and C16:0) and the area of the internal standard (ratio = area C_x / area C15:0) is calculated. The 3-*O*-desacyl-4′-monophosphoryl lipid A quantity corresponding to the sum ratio value on the calibration curve, established with the dilutions of the 3-*O*-desacyl-4′-monophosphoryl lipid A standard, is reported.

The content of 3-*O*-desacyl-4′-monophosphoryl lipid A is not less than 80 per cent and not greater than 120 per cent of the estimated content.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Abacavir and Lamivudine Tablets

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Abacavir and Lamivudine Tablets contain Abacavir Sulfate and Lamivudine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of abacavir, $C_{14}H_{18}N_6O$

95.0 to 105.0% of the stated amount.

Content of lamivudine, $C_8H_{11}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.2 g of abacavir with 50 mL of *water*, filter and use the filtrate.

(2) 0.23% w/v of *abacavir sulfate BPCRS* in *water*.

(3) 0.1% w/v of *lamivudine BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry it in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (1) shows two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The chromatogram obtained with solution (1) shows two principal spots corresponding in position and size to the principal spots in the chromatograms obtained with solutions (2) and (3).

B. In the Assay, the chromatogram obtained with solution (1) shows principal peaks with the same retention time as the principal peaks due to abacavir and lamivudine in the chromatograms obtained with solutions (2) and (3) respectively.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: Dissolve 1.9 g of *ammonium acetate* in 900 mL of *water*, adjust the pH to 3.9 with *glacial acetic acid* and dilute to 1000 mL.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute with the dissolution medium, if necessary, to produce a solution containing the equivalent of 0.067% w/v of abacavir.

(2) 0.078% w/v of *abacavir sulfate BPCRS* and 0.033% w/v of *lamivudine BPCRS* in solution A.

(3) 0.01% w/v of *lamivudine impurity standard BPCRS* and 0.016% w/v of *abacavir sulfate BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of abacavir, $C_{14}H_{18}N_6O$, and lamivudine, $C_8H_{11}N_3O_3S$, in the medium using the declared contents of $C_{14}H_{18}N_6O$, in *abacavir sulfate BPCRS* and of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *lamivudine impurity standard BPCRS* and the retention of abacavir relative to lamivudine is about 2.6;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0.

LIMITS

The amounts of abacavir and lamivudine released are not less than 75% (Q) of the stated amounts.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A.

Solution A: Dissolve 1.9 g of *ammonium acetate* in 900 mL of *water*, adjust the pH to 3.9 with *glacial acetic acid* and dilute to 1000 mL.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of abacavir in 60 mL with the aid of ultrasound for 30 minutes, dilute to 100 mL and filter. Dilute 1 volume of the filtrate to 5 volumes.
(2) Dilute 1 volume of solution (1) to 50 volumes. Further dilute 1 volume to 10 volumes.
(3) 0.01% w/v of *lamivudine impurity standard BPCRS* and 0.016% w/v of *abacavir sulfate BPCRS*.
(4) 0.0001% w/v each of *salicylic acid BPCRS* (lamivudine impurity C) and *cytosine* (lamivudine impurity E).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (YMC ODS-A is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 270 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.025M *ammonium acetate*, adjusted to pH 3.9 with *glacial acetic acid*.

Mobile phase B *methanol*.

Mobile phase C *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-15	95	5	0	isocratic
15-30	95→70	5→30	0	linear gradient
30-38	70	30	0	isocratic
38-60	70→0	30→0	0→100	linear gradient
60-65	0	0	100	column wash
65-66	0→95	0→5	100→0	linear gradient
66-75	95	5	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to lamivudine (retention time about 15 minutes) are lamivudine impurity E, about 0.2; lamivudine impurity F, about 0.3; lamivudine impurity A, about 0.35; lamivudine

www.webofpharma.com

https://thuocngocanh.com/

impurity H, about 0.37; lamivudine impurity C, about 0.39; lamivudine impurity G, about 0.4; lamivudine impurity B, about 0.9; lamivudine impurity J, about 1.5 and abacavir, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *lamivudine impurity standard BPCRS* and the retention of abacavir relative to lamivudine is about 2.6;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0.

LIMITS

Using the chromatogram obtained with solutions (3) and (4), the reference chromatogram supplied with *lamivudine impurity standard BPCRS* and the relative retentions identify any peaks in solution (1) corresponding to the named lamivudine impurities. Multiply any peaks areas corresponding to lamivudine impurity C and lamivudine impurity E by the following correction factors; impurity C, 1.3; impurity E, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to lamivudine impurity J is not greater than 2.5 times the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to lamivudine impurity A is not greater than 1.5 times the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to lamivudine impurities B, C, E, F, G and H is not greater than the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the peak due to abacavir in the chromatogram obtained with solution (2) (0.2%).

The total impurity content is not greater than 2.2%.

Disregard:

any peak corresponding to a lamivudine impurity with an area less than half the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.1%);

any other peak with an area less than half the area of the peak due to abacavir in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A: Dissolve 1.9 g of *ammonium acetate* in 900 mL of *water*, adjust the pH to 3.9 with *glacial acetic acid* and dilute to 1000 mL.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.2 g of abacavir with 60 mL of solution A in a 100-mL amber volumetric flask for 30 minutes, dilute to 100 mL and filter. Dilute 1 volume to 5 volumes.

(2) 0.046% w/v of *abacavir sulfate BPCRS*

(3) 0.02% w/v of *lamivudine BPCRS*.

(4) 0.01% w/v of *lamivudine impurity standard BPCRS* and 0.016% w/v of *abacavir sulfate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the chromatogram obtained with solution (4) closely resembles the reference chromatogram supplied with *lamivudine impurity standard BPCRS* and the retention of abacavir relative to lamivudine is about 2.6;

the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0.

DETERMINATION OF CONTENT

Using solutions (1) and (2), calculate the content of $C_{14}H_{18}N_6O$ in the tablets from the chromatograms obtained using the declared content of $C_{14}H_{18}N_6O$ in *abacavir sulfate BPCRS*.

Using solutions (1) and (3) calculate the content $C_8H_{11}N_3O_3S$ in the tablets from the chromatograms obtained using the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Abacavir Sulfate, excluding impurity A, and Lamivudine.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Abacavir Oral Solution

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Abacavir Oral Solution is a solution containing Abacavir Sulfate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of abacavir, $C_{28}H_{36}N_{12}O_2$

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol (50%)*.

(1) Dilute the oral solution to produce a solution containing the equivalent of 0.2% w/v of abacavir and filter if necessary.

(2) 0.23% w/v of *abacavir sulfate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} HPTLC plates are suitable). Before use, stand the plate in *methanol*, allowing the solvent front to ascend to the top of the plate, remove and heat the plate at 105° for 1 hour.

(b) Use the mobile phase described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 7 cm.

(e) After removal of the plate, dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *methanol*, 6 volumes of 13.5M *ammonia*, 34 volumes of *dichloromethane* and 55 volumes of *acetone*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to abacavir in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity

pH, 3.8 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.1% v/v of *orthophosphoric acid*.

(1) Dilute the oral solution to produce a solution containing the equivalent of 0.02% w/v of abacavir and filter if necessary.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 5 volumes.

(4) Dissolve 2.5 mg of *abacavir for peak identification EPCRS*(containing impurities B and D) in 10.0 mL.

(5) 0.02% w/v of a*bacavir impurity standard BPCRS*.

(6) 0.0001% w/v of *abacavir impurity 1 BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry Shield C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05% v/v of *trifluoroacetic acid*.

Mobile phase B *methanol (85%)*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	95→70	5→30	linear gradient
20-35	70→10	30→90	linear gradient
35-40	10	90	isocratic
40-41	10→0	90→100	column wash
41-50	0	100	column wash
50-51	0→95	100→5	column wash
51-55	95	5	re-equilibration

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (4):

the chromatogram closely resembles the reference chromatogram supplied with *abacavir for peak identification EPCRS*;

the *resolution* between the peaks due to abacavir and abacavir impurity D is at least 1.5.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity C using the chromatogram obtained with solution (5) and the chromatogram supplied with a*bacavir impurity standard BPCRS*.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to abacavir impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to abacavir impurity 1 is not greater than the area of the peak in the chromatogram obtained with solution (6) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all secondary peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.1% v/v of *orthophosphoric acid*.

(1) Dilute the oral solution to produce a solution containing the equivalent of 0.02% w/v of abacavir and filter if necessary.
(2) 0.023% w/v of *abacavir sulfate BPCRS*.
(3) Dissolve 2.5 mg of *abacavir for peak identification EPCRS*(containing impurities B and D) in 10.0 mL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to abacavir and abacavir impurity D is at least 1.5.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{36}N_{12}O_2$ in the oral solution from the chromatograms obtained using the declared content of $C_{28}H_{36}N_{12}O_2$ in *abacavir sulfate BPCRS*.

LABELLING

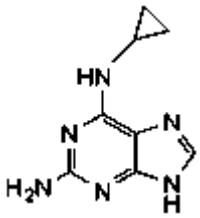
www.webofpharma.com

https://thuocngocanh.com/

The quantity of active ingredient is stated in terms of the equivalent amount of abacavir.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Abacavir Sulfate and the following.



1. N^6-cyclopropyl-1*H*-purine-2,6-diamine.

© Crown Copyright 2022

www.webofpharma.com

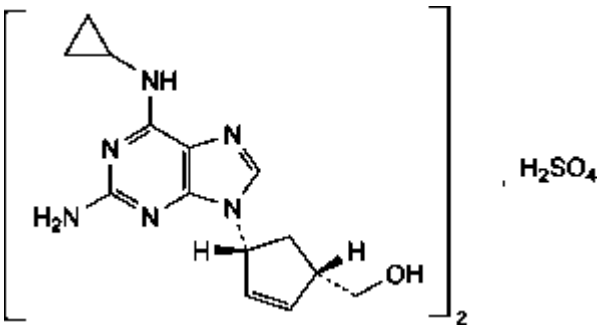
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Abacavir Sulfate

General Notices

(Ph. Eur. monograph 2589)



$C_{28}H_{38}N_{12}O_6S$ 671 *188062-50-2*

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

Preparations

Abacavir Oral Solution

Abacavir Tablets

Abacavir, Zidovudine and Lamivudine Tablets

Abacavir and Lamivudine Tablets

Ph Eur

DEFINITION

Bis[[(1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-enyl]methanol] sulfate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white powder.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *abacavir sulfate CRS*.

B. Enantiomeric purity (see Tests).

C. Solution S (see Tests) gives reaction (a) of sulfates (2.3.1).

TESTS

Solution S

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (2.2.29).

Solution A Mix 0.5 mL of *trifluoroacetic acid R* and 100 mL of *methanol R*.

Solution B Mix 30 volumes of *methanol R*, 30 volumes of *2-propanol R* and 40 volumes of *heptane R*.

Test solution Dissolve 40 mg of the substance to be examined in 30 mL of solution A. Sonicate until dissolution is complete. Add 30 mL of *2-propanol R* and dilute to 100.0 mL with *heptane R*.

Reference solution (a) Dissolve 2 mg of *abacavir for system suitability CRS* (containing impurities A and D) in 1.5 mL of solution A. Sonicate until dissolution is complete. Add 1.5 mL of *2-propanol R* and dilute to 5.0 mL with *heptane R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with solution B. Dilute 1.0 mL of this solution to 10.0 mL with solution B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (10 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *diethylamine R*, *2-propanol R*, *heptane R* (0.1:15:85 *V/V/V*);

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: heptane R, 2-propanol R (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 27	100 → 0	0 → 100
27 - 37	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 286 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with abacavir for system suitability CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and D.

Relative retention With reference to abacavir (retention time = about 17 min): impurity D = about 0.8; impurity A = about 0.9.

System suitability Reference solution (a):

— resolution: minimum 1.5 between the peaks due to impurities D and A; minimum 1.5 between the peaks due to impurity A and abacavir.

Limit:

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and transfer them to low-adsorption, inert glass vials.*

Test solution Dissolve 25 mg of the substance to be examined in water R and dilute to 100.0 mL with the same solvent. Sonicate until dissolution is complete.

Reference solution (a) Dissolve 2.5 mg of abacavir for peak identification CRS (containing impurities B and D) in 10.0 mL of water R.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with water R. Dilute 1.0 mL of this solution to 10.0 mL with water R.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dilute 0.5 mL of *trifluoroacetic acid R* in 1000 mL of *water R*;

— *mobile phase B*: *water R*, *methanol R* (15:85 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 25	95 → 70	5 → 30
25 - 40	70 → 10	30 → 90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *abacavir for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and D.

Relative retention With reference to abacavir (retention time = about 22 min): impurity D = about 1.04; impurity B = about 1.3.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to abacavir.

Limits:

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 60.0 mg.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

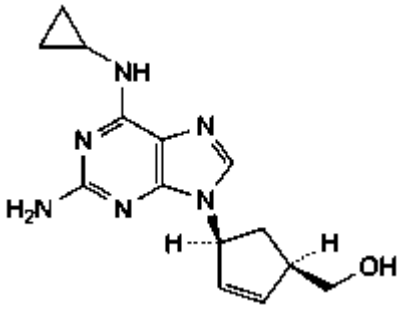
Dissolve 0.300 g in 50 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 33.54 mg of $C_{28}H_{38}N_{12}O_6S$.

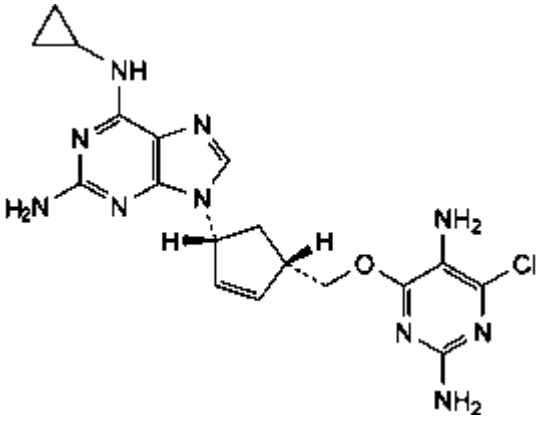
IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F.*



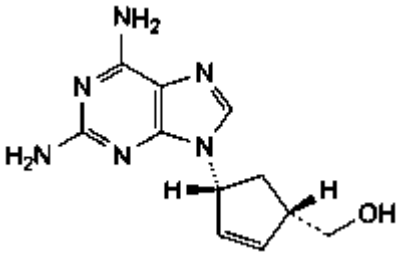
A. [(1*R*,4*S*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-enyl]methanol,



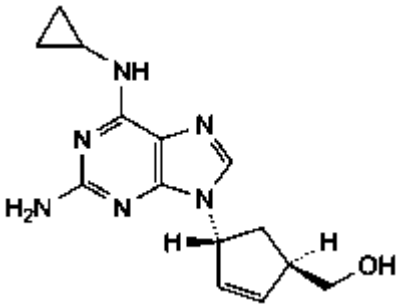
B. 6-(cyclopropylamino)-9-[(1*R*,4*S*)-4-[[(2,5-diamino-6-chloropyrimidin-4-yl)oxy]methyl]cyclopent-2-enyl]-9*H*-purine-2-amine,

www.webofpharma.com

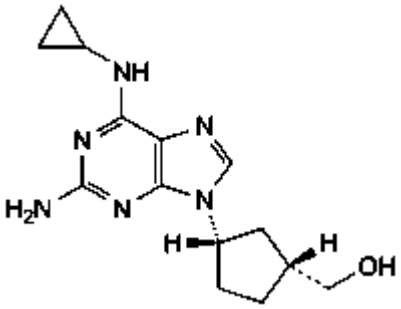
https://thuvienthuocngocanh.com/



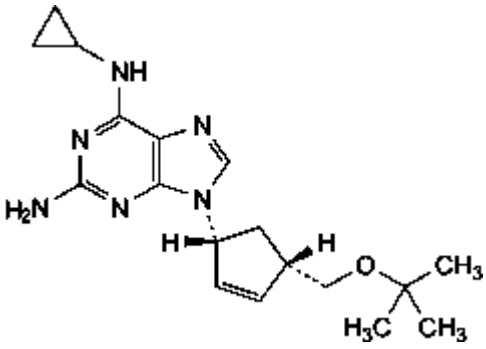
C. [(1*S*,4*R*)-4-(2,6-diamino-9*H*-purin-9-yl)cyclopent-2-enyl]methanol,



D. [(1*R*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopent-2-enyl]methanol,



E. [(1*R*,3*S*)-3-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]cyclopentyl]methanol,



F. 6-(cyclopropylamino)-9-[(1*R*,4*S*)-4-[[(1,1-dimethylethyl)oxy]methyl]cyclopent-2-enyl]-9*H*-purine-2-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Abacavir Tablets

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Abacavir Tablets contain Abacavir Sulfate. They may be coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of abacavir, $C_{14}H_{18}N_6O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.2 g of abacavir with 100 mL, filter and use the filtrate.

(2) 0.23% w/v of *abacavir sulfate BPCRS*.

(3) 0.23% w/v of *abacavir sulfate BPCRS* and 0.2% w/v of *zidovudine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use precoated *silica gel F_{254}* plates (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry it in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The chromatogram obtained with solution (1) shows a principal spot corresponding in position and size to the principal spot in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 75 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid* as the medium at a temperature of 37°.

PROCEDURE

(1) After 45 minutes withdraw a 10-mL sample of the medium and filter. Measure the *absorbance* of the filtered medium, diluted if necessary with 0.1M *hydrochloric acid*, at the maximum at 254 nm using *0.1M hydrochloric acid* in the reference cell, Appendix II B.

(2) Measure the *absorbance* of a solution containing 0.039% w/v of *abacavir sulfate BPCRS* in *0.1M hydrochloric acid* at the maximum at 254 nm using *0.1M hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of abacavir, $C_{14}H_{18}N_6O$, in the medium using the declared content of $C_{14}H_{18}N_6O$ in *abacavir sulfate BPCRS*.

LIMITS

The amount of abacavir released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.1% v/v of *orthophosphoric acid*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.3 g of abacavir with 70 mL for 30 minutes, mix with the aid of ultrasound for 5 minutes; dilute to 100 mL and filter through a 0.45-µm filter (polyvinylidene fluoride is suitable). Dilute 1 volume of the filtrate to 20 volumes.

(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume of the resulting solution to 5 volumes.

(3) Dissolve 2.5 mg of *abacavir for peak identification EPCRS* in 10.0 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry Shield C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase A 0.05% v/v of *trifluoroacetic acid*.

Mobile phase B *methanol* *(85%)*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	95→70	5→30	linear gradient
20-35	70→10	30→90	linear gradient
35-40	10	90	isocratic
40-41	10→0	90→100	column wash
41-50	0	100	column wash
50-51	0→95	100→5	column wash
51-55	95	5	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the chromatogram closely resembles the reference chromatogram supplied with *abacavir for peak identification EPCRS*;

the *resolution* between the peaks due to abacavir and abacavir impurity D is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 8 times the area of the principle peak in the chromatogram obtained with solution (2) (1.6%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, in 0.1% v/v of *orthophosphoric acid*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of abacavir with 70 mL for 30 minutes, dilute to 100 mL and filter. Dilute 1 volume of the filtrate to 5 volumes.

(2) 0.023% w/v of *abacavir sulfate BPCRS*.

(3) Dissolve 2.5 mg of *abacavir for peak identification EPCRS* in 10 mL.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to abacavir and abacavir impurity D is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{18}N_6O$ in the tablets from the chromatograms obtained using the declared content of $C_{14}H_{18}N_6O$ in *abacavir sulfate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of abacavir.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Abacavir Sulfate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Abacavir, Zidovudine and Lamivudine Tablets

General Notices

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

DEFINITION

Abacavir, Zidovudine and Lamivudine Tablets contain Abacavir Sulfate, Zidovudine and Lamivudine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of abacavir, $C_{14}H_{18}N_6O$

95.0 to 105.0% of the stated amount.

Content of zidovudine, $C_{10}H_{13}N_5O_4$

95.0 to 105.0% of the stated amount.

Content of lamivudine, $C_8H_{11}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.2 g of abacavir with 50 mL of *water*, filter and use the filtrate.

(2) 0.2% w/v of *zidovudine BPCRS* in *water*.

(3) 0.23% w/v of *abacavir sulfate BPCRS* in *water*.

(4) 0.1% w/v of *lamivudine BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use precoated *silica gel F_{254}* plates (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry it in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (1) shows three clearly separated spots.

CONFIRMATION

The chromatogram obtained with solution (1) shows three spots corresponding in position, colour and size to the spots in the chromatograms obtained with solutions (2), (3) and (4).

B. In the Assay, the chromatogram obtained with solution (1) shows principal peaks with the same retention time as the principal peaks due to abacavir, zidovudine and lamivudine in the chromatograms obtained with solutions (2), (3) and (4) respectively.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 10 mL sample of the medium and filter.

(2) Dissolve suitable quantities of *abacavir sulfate BPCRS*, *zidovudine BPCRS* and *lamivudine BPCRS* in solvent A, described under Related substances, to produce the same concentrations as that expected for solution (1).

(3) 0.075% w/v of *zidovudine and lamivudine impurity standard BPCRS* and 0.025% w/v of *abacavir sulfate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of abacavir, $C_{14}H_{18}N_6O$, zidovudine, $C_{10}H_{13}N_5O_4$, and lamivudine, $C_8H_{11}N_3O_3S$, in the medium using the declared content of $C_{14}H_{18}N_6O$ *abacavir sulfate BPCRS*, the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS* and the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

LIMITS

The amounts of abacavir, zidovudine and lamivudine released are not less than 75% (Q) of the stated amounts.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

SOLVENT A

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 1.9 g of *ammonium acetate* in 900 mL of *water*, adjust the pH to 3.9 with *glacial acetic acid* and dilute to 1000 mL.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1g of abacavir in 60 mL with the aid of ultrasound for 30 minutes, dilute to 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.002% w/v of *thymine*.

(5) 0.075% w/v of *zidovudine and lamivudine impurity standard BPCRS* and 0.025% w/v of *abacavir sulfate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (YMC ODS-A is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.025M *ammonium acetate*, the pH adjusted to 3.9 with *glacial acetic acid*.

Mobile phase B *methanol*.

Mobile phase C *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-15	95	5	0	isocratic
15-30	95→70	5→30	0	linear gradient
30-38	70	30	0	isocratic
38-60	70→0	30→0	0→100	change of solvent
60-65	0	0	100	washing column
65-66	0→95	0→5	100→0	change in solvent
66-75	95	5	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

www.webofpharma.com

https://thuocngocanh.com/

the chromatogram obtained with solution (5) closely resembles the reference chromatogram supplied with *zidovudine and lamivudine impurity standard BPCRS* and the retention of abacavir relative to zidovudine is about 1.2*;*

the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0;

the *resolution* between the peaks due to lamivudine and thymidine is at least 2.0;

the *resolution* between the peaks due to zidovudine and zidovudine impurity B is at least 4.0;

the *resolution* between the peaks due to zidovudine and abacavir is at least 1.5.

LIMITS

Using the chromatogram obtained with solution (5) and the reference chromatogram supplied with *zidovudine and lamivudine impurity standard BPCRS* identify any peaks in solution (1) corresponding to the named lamivudine and zidovudine impurities.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to thymine (zidovudine impurity C) is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2.0%);

the area of any peak corresponding to zidovudine impurity B is not greater than the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to zidovudine impurity G (retention relative to zidovudine about 1.4) is not greater than 0.5 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to zidovudine impurity 1 (eluting between lamivudine impurity G and zidovudine impurity C) is not greater than 0.4 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to lamivudine impurity A is not greater than 3 times the area of the peak due to lamivudine in the chromatogram obtained with solution (3) (0.3%);

the area of any peak corresponding to a named lamivudine impurity is not greater than 0.2 times the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (0.2%);

the area of any peak corresponding to a named zidovudine impurity is not greater than 0.2 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the peak due to abacavir in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the named zidovudine impurities is not greater than 4 times the area of the peak due to zidovudine in the chromatogram obtained with solution (2) (4.0%);

the sum of the areas of all the named lamivudine impurities is not greater than the area of the peak due to lamivudine in the chromatogram obtained with solution (2) (1.0%);

www.webofpharma.com

https://thuocngocanh.com/

the sum any other *secondary peaks* is not greater than the area of the peak due to abacavir in the chromatogram obtained with solution (2) (1.0%);

Disregard any peak with an area less than the area of the peak due to abacavir in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions dissolved in solvent A described under Related substances.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of abacavir with 50 mL of solvent A in a 100 mL amber volumetric flask for 30 minutes, dilute to 100 mL and filter. Dilute 1 volume to 5 volumes.

(2) 0.023% w/v of *abacavir sulfate BPCRS*

(3) 0.02% w/v of *zidovudine BPCRS*.

(4) 0.01% w/v of *lamivudine BPCRS*.

(5) 0.075% w/v of *zidovudine and lamivudine impurity standard BPCRS* and 0.025% w/v of *abacavir sulfate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (5) closely resembles the reference chromatogram supplied with *zidovudine and lamivudine impurity standard BPCRS* and the retention of abacavir relative to Zidovudine is about 1.2*;*

the *resolution* between the peaks due to lamivudine impurity B and lamivudine is at least 2.0;

the *resolution* between the peaks due to lamivudine and thymidine is at least 2.0;

the *resolution* between the peaks due to zidovudine and zidovudine impurity B is at least 4.0;

the *resolution* between the peaks due to zidovudine and abacavir is at least 1.5.

DETERMINATION OF CONTENT

Using solutions (1) and (2), calculate the total content of $C_{14}H_{18}N_6O$ in the tablets from the chromatograms obtained using the declared content of $C_{14}H_{18}N_6O$ in *abacavir sulfate BPCRS*.

Using solutions (1) and (3), calculate the total content of $C_{10}H_{13}N_5O_4$ in the tablets from the chromatograms obtained using the declared content of $C_{10}H_{13}N_5O_4$ in *zidovudine BPCRS*.

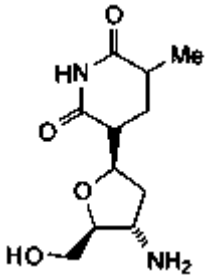
Using solutions (1) and (4) calculate the total content $C_8H_{11}N_3O_3S$ in the tablets from the chromatograms obtained using the declared content of $C_8H_{11}N_3O_3S$ in *lamivudine BPCRS*.

IMPURITIES

www.webofpharma.com

https://thuocngocanh.com/

The impurities limited by the requirements of this monograph include impurities, A, B, C, E, F, G, H and J listed under Lamivudine, impurities B, C, E and G listed under Zidovudine and the following:



1. 1-[(2*R*,4*S*,5*S*)-4-amino-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidin-2,4(1*H*,3*H*)-dione.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acacia

General Notices

(Ph. Eur. monograph 0307)

Action and use

Bulk-forming laxative; excipient.

When Powdered Acacia is prescribed or demanded, material complying with the requirements below with the exception of Identification test A shall be dispensed or supplied.

Ph Eur

DEFINITION

Air-hardened, gummy exudate flowing naturally from or obtained by incision of the trunk and branches of *Acacia senegal* L. Willd. (syn. *Senegalia senegal* (L.) Britton), other species of *Acacia* of African origin and *Acacia seyal* Delile.

CHARACTERS

It is almost completely but very slowly soluble, after about 2 h, in twice its mass of water leaving only a very small residue of vegetable particles; the liquid obtained is colourless or yellowish, dense, viscous, adhesive, translucent and weakly acid to blue litmus paper. It is practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. It occurs as yellowish-white, yellow or pale amber, sometimes with a pinkish tint, friable, opaque, spheroidal, oval or reniform pieces (tears) of a diameter from about 1-3 cm, frequently with a cracked surface, easily broken into irregular, whitish or slightly yellowish angular fragments with a conchoidal fracture and a glassy and transparent appearance. In the centre of an unbroken tear there is sometimes a small cavity.

B. Microscopic examination (*2.8.23*). The powder is white or yellowish-white. Examine under a microscope using *ethanol (96 per cent) R*. The powder shows the following diagnostic characters: angular, irregular, colourless, transparent fragments. Only traces of starch or plant tissues are visible. No stratified membrane is apparent.

C. Examine the chromatograms obtained in the test for glucose and fructose.

Results See below the sequence of zones present in the chromatograms obtained with reference solution (a) and the test solution.

www.webofpharma.com

https://thuocngocanh.com/

Top of the plate	
	3 blue zones, very faint
Rhamnose: a greenish-brown zone	A greenish-brown zone, very faint to equivalent (rhamnose)
Xylose: a brownish-grey zone	
_____	_____
Arabinose: a brownish-grey zone	A brownish-grey zone, intense (arabinose)
Glucose: a greyish-blue zone	
Galactose: a greyish-blue zone	A greyish-blue zone, intense (galactose)
_____	_____
	1 or 2 brownish-grey zones, very faint to equivalent
	1 or 2 blue zones, faint to equivalent
Reference solution (a)	**Test solution**

D. Dissolve 1 g of the powdered herbal drug (355) (2.9.12) in 2 mL of *water R* by stirring frequently for 2 h. Add 2 mL of *ethanol (96 per cent) R*. After shaking, a white gelatinous mucilage is formed that becomes fluid upon addition of 10 mL of *water R*.

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 3.0 g of the powdered herbal drug (355) (2.9.12) in 25 mL of water R by stirring for 30 min. Allow to stand for 30 min and dilute to 30 mL with water R.

Insoluble matter

Maximum 0.5 per cent.

To 5.0 g of the powdered herbal drug (355) (2.9.12) add 100 mL of water R and 14 mL of dilute hydrochloric acid R, boil gently for 15 min, shaking frequently and filter while hot through a tared sintered-glass filter (2.1.2). Wash with hot water R and dry at 100-105 °C. The residue weighs a maximum of 25 mg.

Glucose and fructose

High-performance thin-layer chromatography (2.8.25).

Test solution To 0.1 g of the powdered herbal drug (355) (2.9.12) in a thick-walled centrifuge tube, add 2 mL of a 100 g/L solution of trifluoroacetic acid R and shake vigorously. Stopper the tube and heat the mixture at 120 °C for 1 h. Centrifuge, transfer 1 mL of the clear supernatant into a 10 mL flask and add 5 mL of methanol R.

Reference solution (a) Dissolve 5 mg of arabinose R, 5 mg of galactose R, 5 mg of glucose R, 5 mg of rhamnose R and 5 mg of xylose R in 1 mL of water R and dilute to 10.0 mL with methanol R.

Reference solution (b) Dilute 2.5 mL of reference solution (a) to 10.0 mL with methanol R.

Reference solution (c) Dissolve 5 mg of galactose R and 5 mg of glucose R in 1 mL of water R and dilute to 10 mL with methanol R.

Intensity marker Galactose.

Plate TLC silica gel F_{254} plate R (2-10 µm).

Mobile phase water R, acetonitrile R (15:85 *V/V*).

Application 4 µL of the test solution and reference solutions (a) and (b), and 2 µL of reference solution (c), as bands of 8 mm.

Development A 70 mm from the lower edge of the plate, in an unsaturated tank.

Drying A In air.

Development B 70 mm from the lower edge of the plate, in an unsaturated tank, using freshly prepared mobile phase.

Drying B In air.

Detection Treat with a solution prepared as follows: dissolve 4 g of diphenylamine R and 4 mL of aniline R in 160 mL of acetone R and add phosphoric acid R until the precipitate formed dissolves again (about 30 mL). Heat at 120 °C for 5-10 min and examine in daylight.

System suitability Reference solution (c):

www.webofpharma.com

https://thuocngocanh.com/

— the chromatogram shows in the middle third 2 distinct zones, which may be touching; the lower zone (galactose) and the upper zone (glucose) are greyish-blue.

Results The chromatogram obtained with the test solution shows no greyish-blue zone and no reddish zone between the zones due to galactose and arabinose in the chromatogram obtained with reference solution (a).

Starch, dextrin and agar

To 10 mL of solution S, previously boiled and cooled, add 0.1 mL of *0.05 M iodine*. No blue or reddish-brown colour develops.

Sterculia gum

A. Place 0.2 g of the powdered herbal drug (355) (*2.9.12*) in a 10 mL ground-glass-stoppered cylinder graduated in 0.1 mL. Add 10 mL of *ethanol (60 per cent V/V) R* and shake. Any gel formed occupies a maximum of 1.5 mL.
B. To 1.0 g of the powdered herbal drug (355) (*2.9.12*) add 100 mL of *water R* and shake. Add 0.1 mL of *methyl red solution R*. Not more than 5.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Tannins

To 10 mL of solution S add 0.1 mL of *ferric chloride solution R1*. A gelatinous precipitate is formed, but neither the precipitate nor the liquid is dark blue.

Tragacanth

Examine the chromatograms obtained in the test for glucose and fructose.

Results The chromatogram obtained with the test solution shows no faint to intense brownish-grey zone corresponding to the zone due to xylose in the chromatogram obtained with reference solution (a).

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 1.000 g of the powdered herbal drug (355) (*2.9.12*) by drying in an oven at 105 °C.

Total ash (*2.4.16*)

Maximum 4.0 per cent.

Microbial contamination

TAMC: acceptance criterion 10^4 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^4 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

FUNCTIONALITY-RELATED CHARACTERISTICS

www.webofpharma.com

https://thuocngocanh.com/

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for acacia used as a viscosity-increasing agent and/or suspending agent in aqueous preparations.

Apparent viscosity

Determine the dynamic viscosity using a capillary viscometer (2.2.9) or a rotating viscometer (2.2.10) on a 100 g/L solution of acacia (dried substance).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

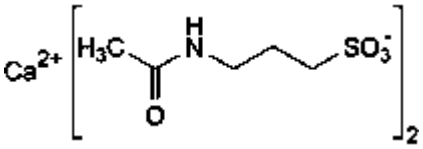
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acamprosate Calcium

General Notices

(Ph. Eur. monograph 1585)



$C_{10}H_{20}CaN_2O_8S_2$ 400.5 *77337-73-6*

Action and use

Treatment of alcoholism.

Preparation

Acamprosate Gastro-resistant Tablets

Ph Eur

DEFINITION

Calcium bis(3-acetamidopropane-1-sulfonate).

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *acamprosate calcium CRS*.

B. It gives reaction (a) of calcium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.5 to 7.0 for solution S.

Impurity A

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.400 g of the substance to be examined in *distilled water R* and dilute to 20.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *borate buffer solution pH 10.4 R*. Introduce 3.0 mL of this solution into a 25 mL ground-glass-stoppered tube and add 0.15 mL of a freshly prepared 5 g/L solution of *fluorescamine R* in *acetonitrile R*. Shake immediately and vigorously for 30 s. Heat in a water-bath at 50 °C for 30 min. Cool under a stream of cold water. Centrifuge and filter the supernatant through a membrane filter (nominal pore size 0.45 µm).

Reference solution Dissolve 50.0 mg of *acamprosate impurity A CRS* in *distilled water R* and dilute to 200.0 mL with the same solvent. Dilute 0.4 mL of the solution to 100.0 mL with *borate buffer solution pH 10.4 R*. Introduce 3.0 mL of this solution into a 25 mL ground-glass-stoppered tube. Proceed as described for the test solution, starting from ‘and add 0.15 mL of a freshly prepared 5 g/L solution of *fluorescamine R*'.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *methanol R*, *0.1 M phosphate buffer solution pH 6.5 R* (10:10:80 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 261 nm.

Injection 20 µL.

Run time 6 times the retention time of impurity A derivative.

www.webofpharma.com

https://thuocngocanh.com/

Retention time Fluorescamine = about 4 min; impurity A derivative = about 8 min; acamprosate is not detected by this system.

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.05 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.100 g of the substance to be examined in 8 mL of *water R* using sonication and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 3.0 mL of test solution (a) to 100.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (b) Dissolve 30.0 mg of *acamprosate calcium CRS* in 20 mL of *water R* using sonication and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dissolve 10 mg of *calcium bis(formyl homotaurine) R* (corresponding to about 9 mg of impurity B) in 1 mL of test solution (a) and dilute to 100 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm).

Mobile phase Mix 5 mL of *triethylamine R* and about 900 mL of *water for chromatography R*, adjust to pH 4.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (c).

Run time 2.5 times the retention time of acamprosate.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

Relative retention With reference to acamprosate (retention time = about 9 min): calcium = about 0.4; impurity B = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity B and acamprosate.

www.webofpharma.com

https://thuocngocanh.com/

Calculation of percentage contents:

— for each impurity, use the concentration of acamprosate calcium in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.03 per cent; disregard the peak due to calcium.

Loss on drying (2.2.32)

Maximum 0.4 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 20 µL of test solution (b) and reference solution (b).

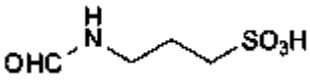
Calculate the content of $C_{10}H_{20}CaN_2O_8S_2$ taking into account the assigned content of *acamprosate calcium CRS*.

IMPURITIES

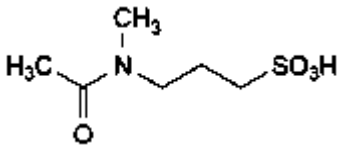
Specified impurities *A*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C*.

A. 3-aminopropane-1-sulfonic acid (homotaurine),



B. 3-formamidopropane-1-sulfonic acid (formyl homotaurine),



C. 3-(*N*-methylacetamido)propane-1-sulfonic acid.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acamprosate Gastro-resistant Tablets

General Notices

Gastro-resistant Acamprosate Tablets

Action and use

Treatment of alcoholism.

DEFINITION

Acamprosate Gastro-resistant Tablets contain Acamprosate Calcium. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of acamprosate calcium, $C_{10}H_{20}CaN_2O_8S_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

B. The powdered tablets yield reaction A characteristic of *calcium salts*, Appendix VI.

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

First stage

(a) Use Apparatus 1, rotating the basket at 180 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 2 hours, withdraw a 20-mL sample of the medium, filter through a 0.45-µm filter and dilute, if necessary, to produce a solution expected to contain 0.037% w/v of Acamprosate Calcium.

(2) 0.00185% w/v of *acamprosate calcium BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Synergi Hydro RP is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

To 850 mL of a solution containing 140.5 mg of *sodium perchlorate* and 170.95 mg of *tetrabutylammonium perchlorate* add 100 mL of *methanol R2* and dilute to 1000 mL with *water*.

DETERMINATION OF CONTENT

Calculate the total content of $C_{10}H_{20}CaN_2O_8S_2$ in the medium using the declared content of $C_{10}H_{20}CaN_2O_8S_2$in *acamprosate calcium BPCRS*.

LIMITS

The amount of Acamprosate Calcium released is not more than 5% of the stated amount.

Final stage

Buffer pH 6.8 Add 150 mL of 2M *sodium hydroxide* in sufficient 0.1M *citric acid* to produce 1000 mL, adjust the pH to 6.8, if necessary, with 0.5M *citric acid*.

(a) Use Apparatus 1, rotating the basket at 180 revolutions per minute.

(b) Replace the 0.1M *hydrochloric acid* in the vessel with 900 mL of buffer pH 6.8, previously held and maintained at 37°.

PROCEDURE

(1) After 2 hours, withdraw a 20-mL sample of the medium, filter through a 0.45-µm filter and dilute, if necessary, to produce a solution expected to contain 0.037% w/v of Acamprosate Calcium.

(2) 0.037% w/v of *acamprosate calcium BPCRS* in buffer pH 6.8.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{10}H_{20}CaN_2O_8S_2$ in the medium using the declared content of $C_{10}H_{20}CaN_2O_8S_2$in *acamprosate calcium BPCRS*.

LIMITS

The amount of Acamprosate Calcium released is not less than 75% (Q) of the stated amount.

Impurity A (homotaurine)

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Remove the tablet coating from 5 tablets by stirring with three 50-mL quantities of *acetone*. Allow the cores to dry at room temperature. Stir a quantity of the powdered tablets containing 333 mg of Acamprosate Calcium with 50 mL of *borate buffer solution pH 10.4* for 10 minutes and filter through a 0.45-µm filter. Dilute 3 mL of this solution to 20 mL with *borate buffer solution pH 10.4*. Place 3.0 mL of the solution obtained in a 25-mL ground-glass-stoppered tube. Add 0.15 mL of a freshly prepared 0.5% w/v solution of *fluorescamine* in *acetonitrile*. Shake immediately and vigorously for 30 seconds. Place in a water-bath at 50° for 30 min. Cool under a stream of cold water. Filter the supernatant liquid through a suitable filter.

(2) Dissolve 10 mg of *acamprosate impurity A EPCRS* in *borate buffer solution pH 10.4* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL *with* *borate buffer solution pH 10.4*. Treat 3.0 mL of this solution in the same way as solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) with a stainless steel pre-column (7.5 cm × 4.6 mm) both packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 261 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 6 times the retention time of impurity A.

MOBILE PHASE

10 volumes of *acetonitrile*, 10 mL of *methanol* and 80 volumes of *0.1M phosphate buffer solution pH 6.5*.

When the chromatograms are recorded under the prescribed conditions the retention time of fluorescamine is about 4 minutes and impurity A is about 8 minutes. Acamprosate is not detected.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Weigh and powder 20 tablets. Shake, with the aid of ultrasound, a quantity of the powdered tablets containing 333 mg of Acamprosate Calcium with 150 mL of mobile phase, dilute to 200 mL and filter through a 0.45-µm filter. Dilute 1 volume of the resulting solution to 5 volumes.

(2) 0.033% w/v of *acamprosate calcium BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (10 cm × 4.6 mm) with a stainless steel pre-column (7.5 cm × 4.6 mm) both packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

To 850 mL of a solution containing 140.5 mg of *sodium perchlorate* and 342 mg of *tetrabutylammonium perchlorate* add 100 mL of *methanol R2* and dilute to 1000 mL with *water*.

SYSTEM SUITABILITY

Inject solution (2) five times. The test is not valid unless the relative standard deviation of the area of the principal peak is at most 2.0%.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{20}CaN_2O_8S_2$ in the tablets from the chromatogram obtained and using the declared content of $C_{10}H_{20}CaN_2O_8S_2$ in *acamprosate calcium BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

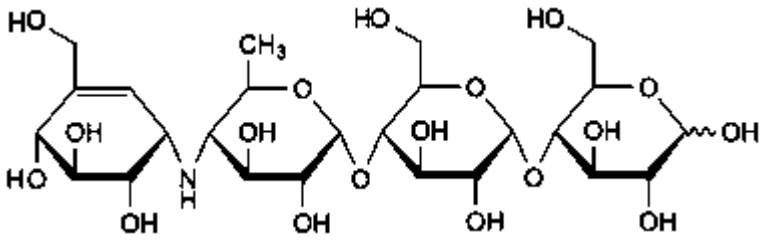
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acarbose

General Notices

(Ph. Eur. monograph 2089)



$C_{25}H_{43}NO_{18}$ 646 *56180-94-0*

Action and use

Alpha-glucosidase inhibitor; treatment of diabetes mellitus.

Ph Eur

DEFINITION

O-4,6-Dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucopyranose, which is produced by certain strains of *Actinoplanes utahensis*.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish, hygroscopic, amorphous powder.

Solubility

Very soluble in water, soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *acarbose for identification CRS*.

www.webofpharma.com

https://nhathuocngocanh.com/

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

pH (*2.2.3*)

5.5 to 7.5 for solution S.

Specific optical rotation (*2.2.7*)

+ 168 to + 183 (anhydrous substance).

Dilute 2.0 mL of solution S to 10.0 mL with *water R*.

Absorbance (*2.2.25*)

Maximum 0.15 at 425 nm for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.200 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *acarbose CRS* in 5.0 mL of *water R*.

Reference solution (b) Dissolve the contents of a vial of *acarbose for peak identification CRS* (acarbose containing impurities A, B, C, D, E, F and G) in 1 mL of *water R*.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 750 volumes of *acetonitrile R1* and 250 volumes of a solution containing 0.60 g/L of *potassium dihydrogen phosphate R* and 0.35 g/L of *disodium hydrogen phosphate dihydrate R*.

Flow rate 2.0 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time 2.5 times the retention time of acarbose.

Identification of impurities Use the chromatogram supplied with *acarbose for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D, E, F and G.

Relative retention With reference to acarbose (retention time = about 16 min): impurity D = about 0.5; impurity B = about 0.8; impurity A = about 0.9; impurity C = about 1.2; impurity E = about 1.7; impurity F = about 1.9; impurity G = about 2.2.

System suitability Reference solution (b):

— the chromatogram obtained is similar to the chromatogram supplied with *acarbose for peak identification CRS*;

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to acarbose.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.63; impurity D = 0.75; impurity E = 1.25; impurity F = 1.25; impurity G = 1.25;

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.5 per cent);

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *impurity A*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent);

— *impurity B*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurities F, G*: for each impurity, not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurity E*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

www.webofpharma.com

https://thuvienthuocngocanh.com/

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{25}H_{43}NO_{18}$ taking into account the assigned content of *acarbose CRS*.

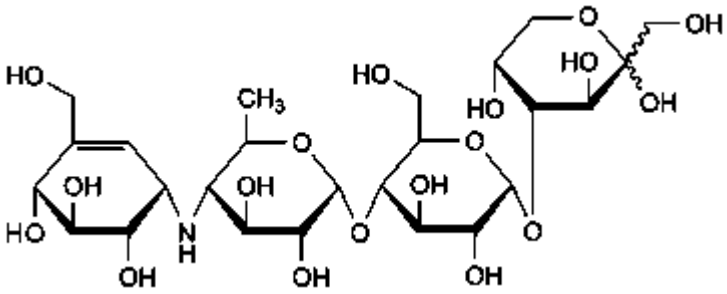
STORAGE

In an airtight container.

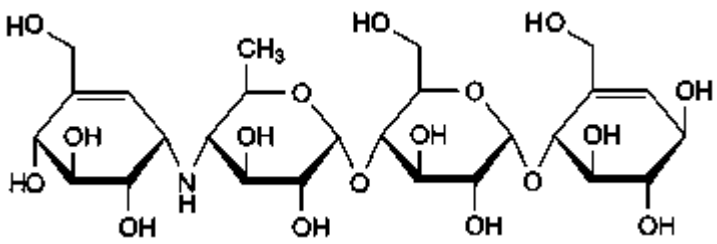
IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H.*



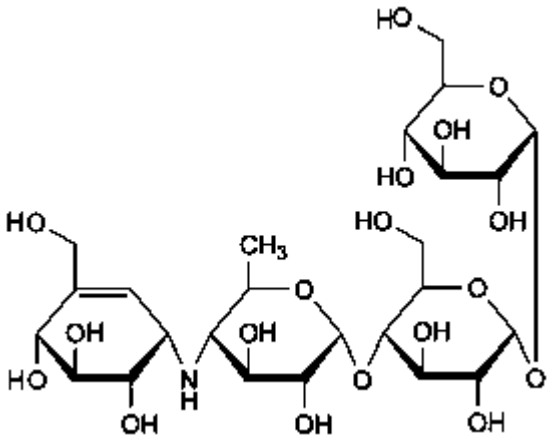
A. *O*-4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-*arabino*-hex-2-ulopyranose,



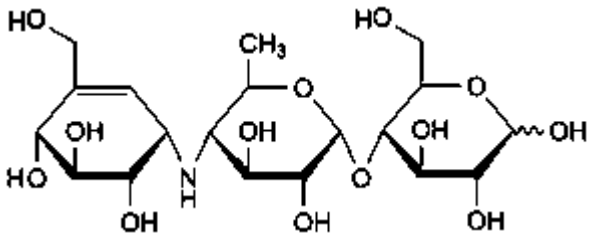
www.webofpharma.com

https://thuocngocanh.com/

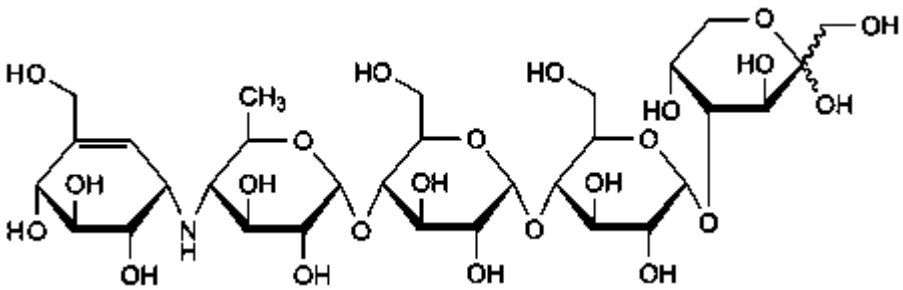
B. (1*R*,4*R*,5*S*,6*R*)-4,5,6-trihydroxy-2-(hydroxymethyl)cyclohex-2-enyl 4-*O*-[4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl]-α-D-glucopyranoside,



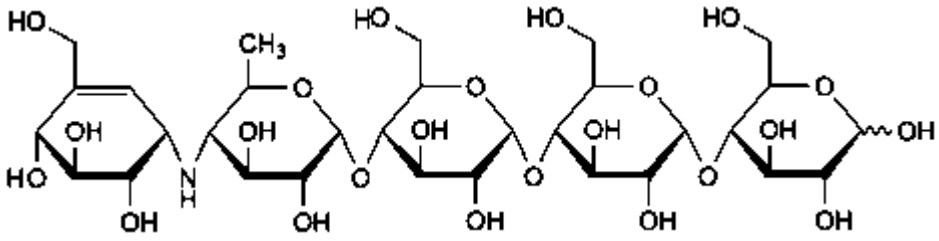
C. α-D-glucopyranosyl 4-*O*-[4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl]-α-D-glucopyranoside,



D. 4-*O*-[4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl]-D-glucopyranose,



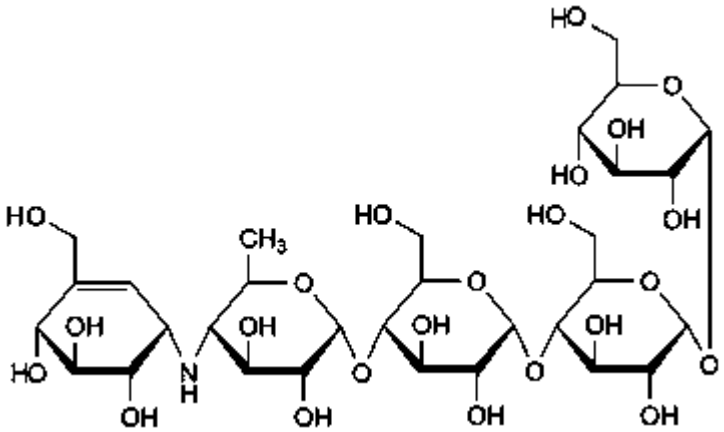
E. *O*-4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-*arabino*-hex-2-ulopyranose (4-*O*-α-acarbosyl-D-fructopyranose),



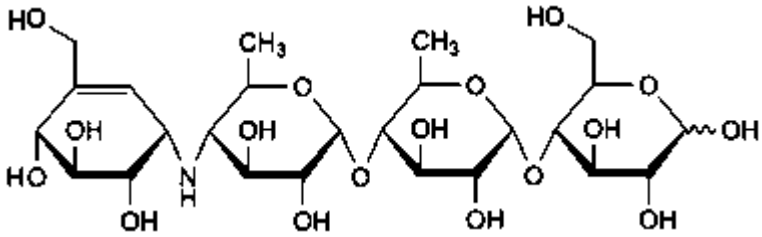
F. *O*-4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucopyranose (4-*O*-α-acarbosyl-D-glucopyranose),

www.webofpharma.com

https://thuocngocanh.com/



G. α-D-glucopyranosyl *O*-4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranoside (α-D-glucopyranosyl α-acarboside),



H. *O*-4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosyl-(1→4)-*O*-6-deoxy-α-D-glucopyranosyl-(1→4)-D-glucopyranose.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acebutolol Capsules

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Acebutolol Capsules contain Acebutolol Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of acebutolol, $C_{18}H_{28}N_2O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum* of a 0.7% w/w dispersion of the contents of the capsules in *potassium chloride*, Appendix II A, is concordant with the *reference spectrum* of Acebutolol hydrochloride *(RS 380)*.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add to a quantity of the contents of the capsules containing the equivalent of 0.4 g of Acebutolol 20 mL of a mixture of equal volumes of *chloroform* and *methanol*, shake for 2 minutes, centrifuge and use the supernatant liquid.
(2) Dilute 3 volumes of solution (1) to 100 volumes with a mixture of equal volumes of *chloroform* and *methanol* and further dilute 1 volume of this solution to 10 volumes with the same mixture of solvents.
(3) Dilute 1 volume of solution (1) to 100 volumes with a mixture of equal volumes of *chloroform* and *methanol* and further dilute 1 volume of this solution to 10 volumes with the same mixture of solvents.

CHROMATOGRAPHIC CONDITIONS

(a) Use a precoated silica gel F_{254} plate (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *dimethylformamide* and 60 volumes of *chloroform*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.3%);

not more than two such spots are more intense than the spot in the chromatogram obtained with solution (3) (0.1%).

Disregard any spot remaining on the line of application.

ASSAY

To a quantity of the mixed contents of 20 capsules containing the equivalent of 0.15 g of Acebutolol add 150 mL of *water*, shake for 10 minutes, add sufficient *water* to produce 250 mL, centrifuge and dilute 10 mL of the supernatant liquid to 100 mL with *water*. To 10 mL of this solution add 10 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 100 mL. Measure the *absorbance* of this solution, Appendix II B, at the maximum at 233 nm and calculate the content of $C_{18}H_{28}N_2O_4$ in the capsules taking 643 as the value of A(1%, 1 cm) at the maximum at 233 nm.

STORAGE

Acebutolol Capsules should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of acebutolol.

© Crown Copyright 2022

www.webofpharma.com

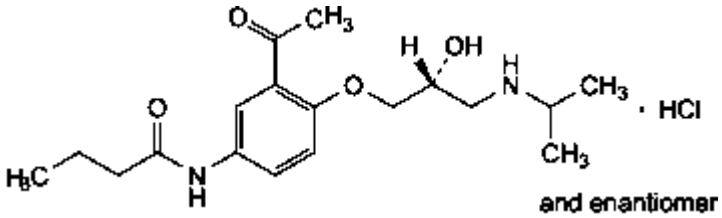
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acebutolol Hydrochloride

General Notices

(Ph. Eur. monograph 0871)



$C_{18}H_{29}ClN_2O_4$ 372.9 *34381-68-5*

Action and use

Beta-adrenoceptor antagonist.

Preparations

Acebutolol Capsules

Acebutolol Tablets

Ph Eur

DEFINITION

N-[3-Acetyl-4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]butanamide hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), very slightly soluble in acetone and in methylene chloride.

mp

www.webofpharma.com

https://thuocngocanh.com/

About 143 °C.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20.0 mg in a 0.1 per cent *V/V* solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid solution. Dilute 5.0 mL of this solution to 100.0 mL with a 0.1 per cent *V/V* solution of *hydrochloric acid R*.

Spectral range 220-350 nm.

Absorption maxima At 233 nm and 322 nm.

Specific absorbance at the absorption maximum 555 to 605 at 233 nm.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *acebutolol hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *acebutolol hydrochloride CRS* in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *pindolol CRS* in *methanol R* and dilute to 20 mL with the same solvent. To 1 mL of this solution add 1 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *perchloric acid R*, *methanol R*, *water R* (5:395:600 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://nhathuocngocanh.com/

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, Method II).

Dissolve 0.5 g in water R and dilute to 10 mL with the same solvent.

pH (2.2.3)

5.0 to 7.0.

Dissolve 0.20 g in carbon dioxide-free water R and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 20.0 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 0.5 mL of this solution to 50.0 mL with mobile phase A.

Reference solution (b) Dissolve the contents of a vial of acebutolol impurity I CRS in 1.0 mL of mobile phase A.

Reference solution (c) Mix 2.0 mL of reference solution (a) and 1.0 mL of reference solution (b) and dilute to 10.0 mL with mobile phase A.

Reference solution (d) Dissolve 5.0 mg of acebutolol impurity C CRS in 10 mL of acetonitrile R and dilute to 25.0 mL with mobile phase A. Dilute 0.5 mL of this solution to 50.0 mL with mobile phase A.

Reference solution (e) Dissolve 5.0 mg of acebutolol impurity B CRS in 10.0 mL of acetonitrile R and dilute to 25.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm,

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm),

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 2.0 mL of phosphoric acid R, and 3.0 mL of triethylamine R and dilute to 1000 mL with water R;

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: mix equal volumes of *acetonitrile R* and mobile phase A;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	98	2
2 - 30.5	98 → 10	2 → 90
30.5 - 41	10	90

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 25 µL.

System suitability Reference solution (c):

— *resolution*: minimum 7.0 between the peaks due to impurity I and acebutolol.

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.2 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *impurity I*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *ethanol (96 per cent) R* and add 1 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 37.29 mg of $C_{18}H_{29}ClN_2O_4$.

www.webofpharma.com

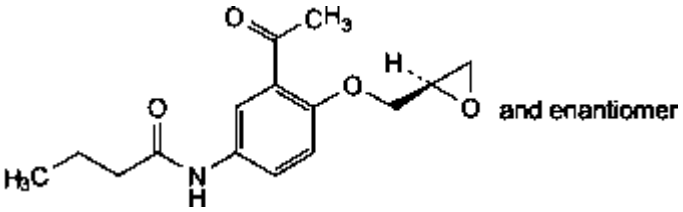
https://thuocngocanh.com/

STORAGE

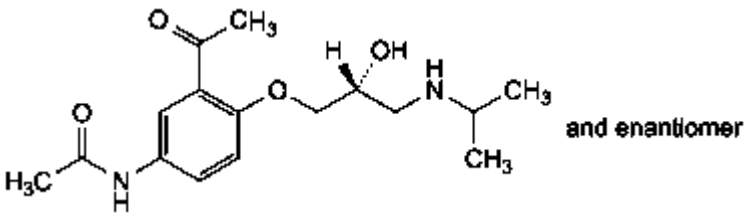
Protected from light.

IMPURITIES

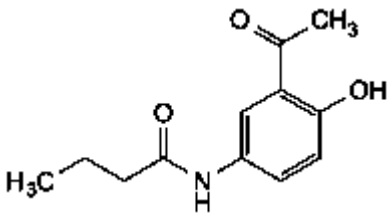
Specified impurities *A, B, C, D, E, F, G, H, I, J, K.*



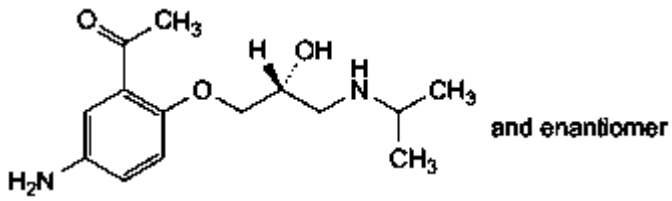
A. *N*-[3-acetyl-4-[(2*RS*)-oxiran-2-ylmethoxy]phenyl]butanamide,



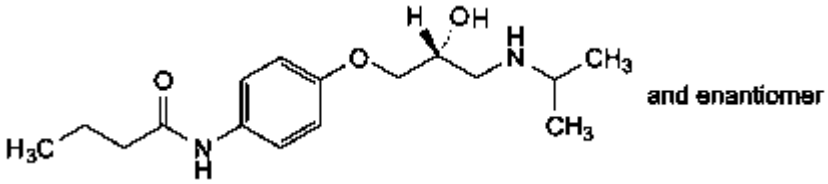
B. *N*-[3-acetyl-4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]acetamide (diacetolol),



C. *N*-(3-acetyl-4-hydroxyphenyl)butanamide,



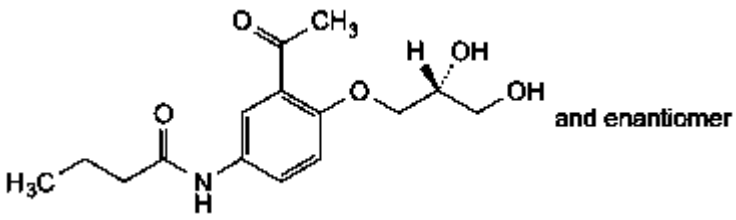
D. 1-[5-amino-2-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]ethanone,



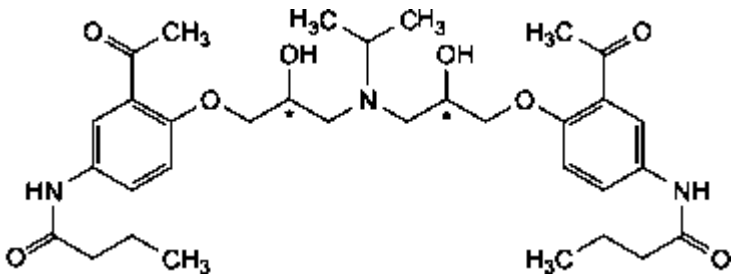
E. *N*-[4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]butanamide,

www.webofpharma.com

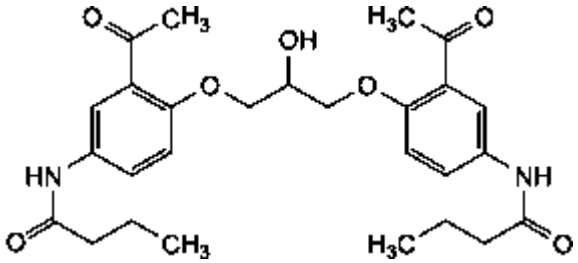
https://thuocngocanh.com/



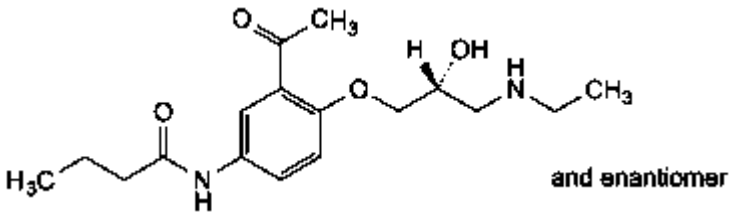
F. *N*-[3-acetyl-4-[(2*RS*)-2,3-dihydroxypropoxy]phenyl]butanamide,



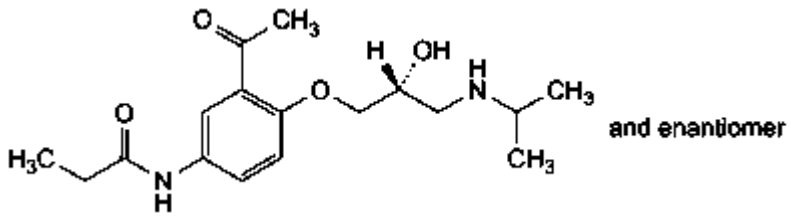
G. *N*,*N*′-[[(1-methylethyl)imino]bis[(2-hydroxypropane-1,3-diyl)oxy(3-acetyl-1,4-phenylene)]]dibutanamide (biamine),



H. *N*,*N*′-[(2-hydroxypropane-1,3-diyl)bis[oxy(3-acetyl-1,4-phenylene)]]dibutanamide,



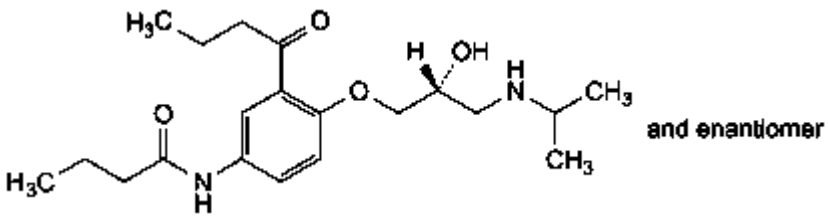
I. *N*-[3-acetyl-4-[(2*RS*)-3-(ethylamino)-2-hydroxypropoxy]phenyl]butanamide,



J. *N*-[3-acetyl-4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]propanamide,

www.webofpharma.com

https://thuocngocanh.com/



and enantiomer

K. *N*-[3-butanoyl-4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]butanamide.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

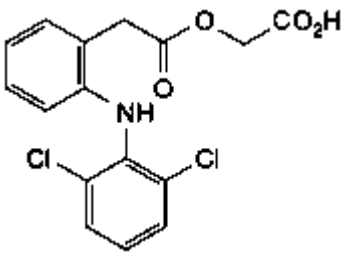
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aceclofenac

General Notices

(Ph. Eur. monograph 1281)



$C_{16}H_{13}Cl_2NO_4$ 354.2 *89796-99-6*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

[[[2-[(2,6-Dichlorophenyl)amino]phenyl]acetyl]oxy]acetic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 50.0 mL with *methanol R*.

Spectral range 220-370 nm.

Absorption maximum 275 nm.

Specific absorbance at the absorption maximum 320 to 350.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison: Ph. Eur. reference spectrum of aceclofenac.

C. Dissolve about 10 mg in 10 mL of *ethanol (96 per cent) R*. To 1 mL of the solution, add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of *potassium ferricyanide R* and a 9 g/L solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 mL of a 10.0 g/L solution of *hydrochloric acid R*. Allow to stand protected from light for 15 min. A blue colour develops and a precipitate is formed.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture Mobile phase A, mobile phase B (30:70 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 21.6 mg of *diclofenac sodium CRS* (impurity A) in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 2.0 mL of the test solution to 10.0 mL with the solvent mixture.

Reference solution (c) Mix 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) and dilute to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 4.0 mg of *aceclofenac impurity F CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (e) Dissolve 2.0 mg of *aceclofenac impurity H CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (f) Mix 1.0 mL of reference solution (b), 1.0 mL of reference solution (d) and 1.0 mL of reference solution (e) and dilute to 100.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (g) Dissolve 5.0 mg of *aceclofenac impurity I CRS* in the solvent mixture and dilute to 50.0 mL with solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (h) Dissolve 4 mg of *aceclofenac for peak identification CRS* (containing impurities B, C, D, E and G) in 2 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent;

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 1.12 g/L solution of *phosphoric acid R* adjusted to pH 7.0 with a 42 g/L solution of *sodium hydroxide R*;

— *mobile phase B*: *water R*, *acetonitrile R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	70 → 50	30 → 50
25 - 30	50 → 20	50 → 80
30 - 50	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL of the test solution and reference solutions (c), (d), (e), (f), (g) and (h).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram supplied with *aceclofenac for peak identification CRS* and the chromatogram obtained with reference solution (h) to identify the peaks due to impurities B, C, D, E and G; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity H; use the chromatogram obtained with reference solution (g) to identify the peak due to impurity I.

Relative retention With reference to aceclofenac (retention time = about 11 min): impurity A = about 0.8; impurity G = about 1.3; impurity H = about 1.5; impurity I = about 2.3; impurity D = about 3.1; impurity B = about 3.2; impurity E = about 3.3; impurity C = about 3.5; impurity F = about 3.7.

System suitability Reference solution (c):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 5.0 between the peaks due to impurity A and aceclofenac.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurities B, C, D, E, G*: for each impurity, not more than the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.2 per cent);

— *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.2 per cent);

— *impurity H*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.15 per cent);

— *impurity I*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (g) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.10 per cent);

— *total*: maximum 0.7 per cent;

— *disregard limit*: 0.25 times the area of the peak due to aceclofenac in the chromatogram obtained with reference solution (f) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 40 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 35.42 mg of $C_{16}H_{13}Cl_2NO_4$.

STORAGE

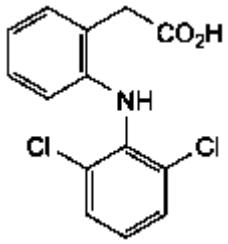
Protected from light.

IMPURITIES

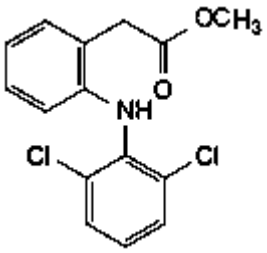
Specified impurities *A, B, C, D, E, F, G, H, I.*

www.webofpharma.com

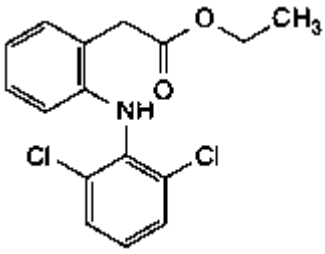
https://thuocngocanh.com/



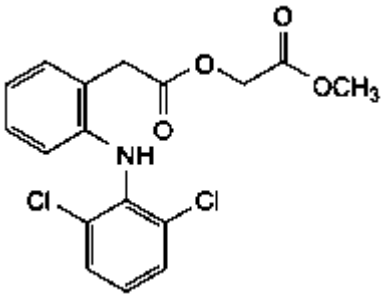
A. [2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid (diclofenac),



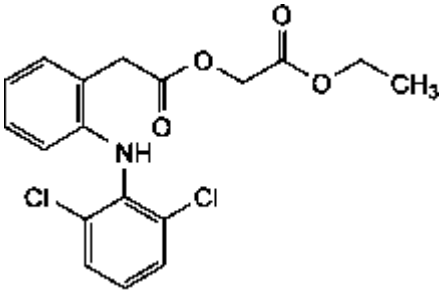
B. methyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (methyl ester of diclofenac),



C. ethyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (ethyl ester of diclofenac),



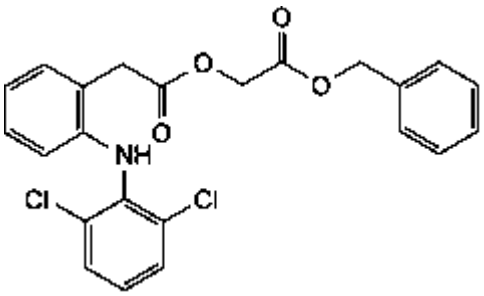
D. methyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (methyl ester of aceclofenac),



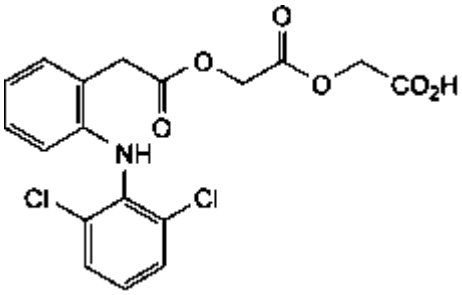
E. ethyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (ethyl ester of aceclofenac),

www.webofpharma.com

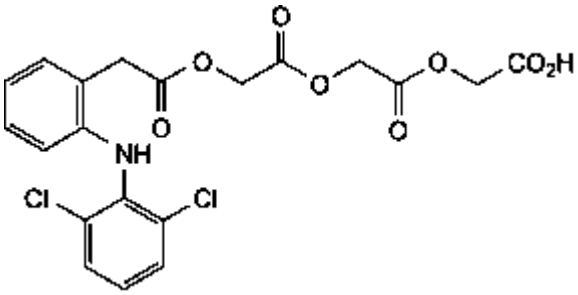
https://thuocngocanh.com/



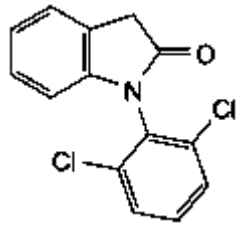
F. benzyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (benzyl ester of aceclofenac),



G. [[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac),



H. [[[[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetyl]oxy]acetyl]oxy]acetic acid (diacetic aceclofenac),



I. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

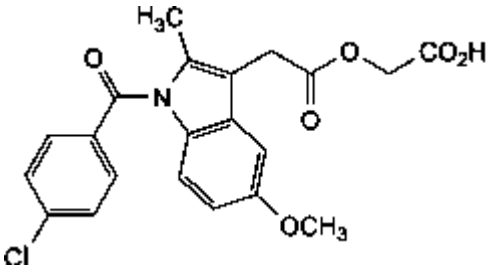
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acemetacin

General Notices

(Ph. Eur. monograph 1686)



$C_{21}H_{18}ClNO_6$ 415.8 *53164-05-9*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

[[[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow or greenish-yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone, slightly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *acemetacin CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in *acetonitrile for chromatography R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dilute 5.0 mL of the test solution to 50.0 mL with *acetonitrile for chromatography R*. Dilute 1.0 mL of this solution to 100.0 mL with *acetonitrile for chromatography R*.

Reference solution (b) Dissolve 5.0 mg of *acemetacin impurity A CRS* and 10.0 mg of *indometacin CRS* (impurity B) in *acetonitrile for chromatography R*, and dilute to 50.0 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 20.0 mL with *acetonitrile for chromatography R*.

Reference solution (d) To 1 mL of reference solution (b), add 10 mL of the test solution and dilute to 20 mL with *acetonitrile for chromatography R*.

Reference solution (e) Dissolve the contents of a vial of *acemetacin impurity mixture CRS* (containing impurities C, D, E and F) in 1.0 mL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of *potassium dihydrogen phosphate R* in 900 mL of *water R*, adjust to pH 6.5 with *1 M sodium hydroxide* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 9	95 → 65	5 → 35

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
9 - 16	65	35
16 - 28	65 → 20	35 → 80
28 - 34	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Identification of impurities:

— use the chromatogram supplied with *acemetacin impurity mixture CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities C, D, E and F;

— use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to acemetacin (retention time = about 15 min): impurity A = about 0.7; impurity B = about 0.9; impurity F = about 1.2; impurity C = about 1.3; impurity D = about 1.5; impurity E = about 2.2.

System suitability Reference solution (d):

— *peak-to-valley ratio*: minimum 15, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to acemetacin.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.3; impurity D = 1.4; impurity F = 1.3;

— *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *impurities C, D, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 20 mL of *acetone R* and add 10 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

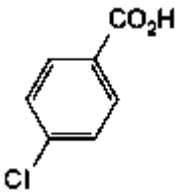
1 mL of *0.1 M sodium hydroxide* is equivalent to 41.58 mg of $C_{21}H_{18}ClNO_6$.

STORAGE

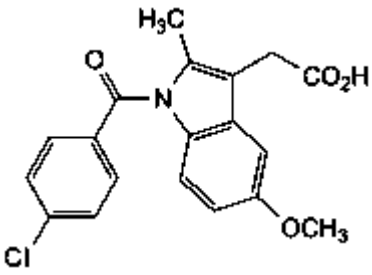
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*



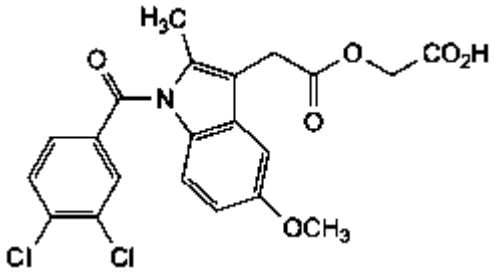
A. 4-chlorobenzoic acid,



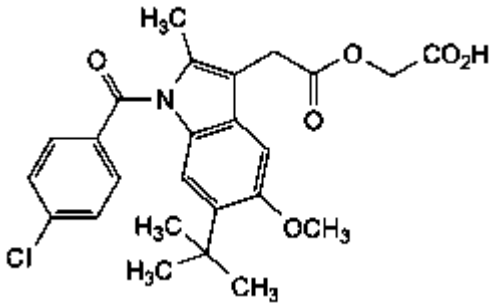
B. [1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid (indometacin),

www.webofpharma.com

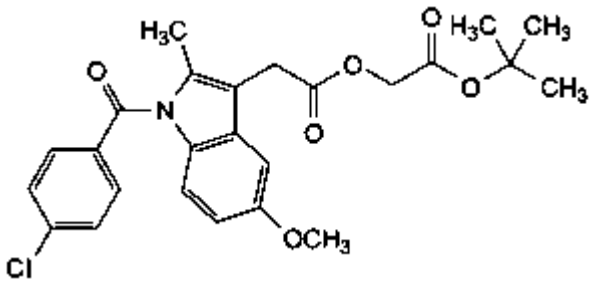
https://thuocngocanh.com/



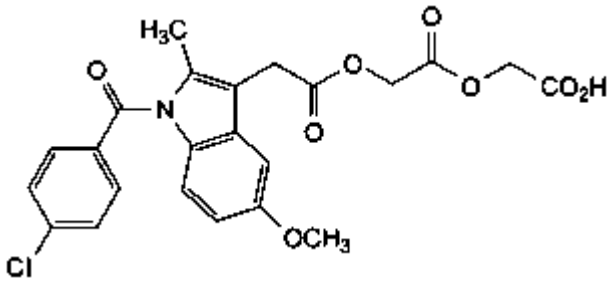
C. [[[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetic acid,



D. [[[1-(4-chlorobenzoyl)-6-(1,1-dimethylethyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetic acid,



E. 1,1-dimethylethyl [[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetate,



F. [[[[[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetyl]oxy]acetyl]oxy]acetic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

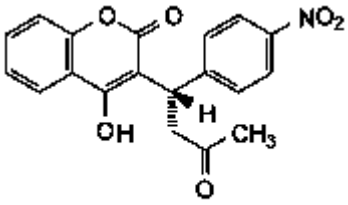
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acenocoumarol

General Notices



and enantiomer

$C_{19}H_{15}NO_6$ 353.3 *152-72-7*

Action and use

Vitamin K epoxide reductase inhibitor; oral anticoagulant.

Preparation

Acenocoumarol Tablets

DEFINITION

Acenocoumarol is (*RS*)-4-hydroxy-3-(1-*p*-nitrophenyl-3-oxobutyl)coumarin. It contains not less than 98.5% and not more than 100.5% of $C_{19}H_{15}NO_6$, calculated with reference to the dried substance.

CHARACTERISTICS

An almost white to buff powder.

Practically insoluble in *water* and in *ether*; slightly soluble in *ethanol (96%)*. It dissolves in aqueous solutions of the alkali hydroxides. It exhibits polymorphism.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of acenocoumarol *(RS 001)*. If the spectra are not concordant, dissolve 0.1 g of the substance being examined in 10 mL of *acetone* and add *water* drop wise until the solution becomes turbid. Heat on a water bath until the solution is clear and allow to stand. Filter, wash the crystals with a mixture of equal volumes of *acetone* and *water* and dry at 100° at a pressure of 2 kPa for 30 minutes. Prepare a new spectrum of the residue.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Clarity and colour of solution

A. A 2.0% w/v solution in *acetone* is *clear*, Appendix IV A.

B. The *absorbance* of a 4-cm layer of a 2.0% w/v solution in *acetone* at 460 nm is not more than 0.12, Appendix II B.

C. A 2.0% w/v solution in 0.1M *sodium hydroxide* is *clear*, Appendix IV A, and yellow.

Light absorption

Absorbance of a 0.001% w/v solution in a mixture of 1 volume of 1M *hydrochloric acid* and 9 volumes of *methanol* at the maximum at 306 nm, 0.50 to 0.54, calculated with reference to the dried substance, Appendix II B.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *acetone*.

(1) 2.0% w/v of the substance being examined.

(2) 0.0020% w/v of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 50 volumes of *cyclohexane* and 50 volumes of *dichloromethane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.1%).

Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 0.6 g in 50 mL of *acetone* and titrate with *0.1M sodium hydroxide VS* using *bromothymol blue solution R3* as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of sodium hydroxide required. Each mL of *0.1M sodium hydroxide VS* is equivalent to 35.33 mg of $C_{19}H_{15}NO_6$.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acenocoumarol Tablets

General Notices

Action and use

Vitamin K epoxide reductase inhibitor; oral anticoagulant.

DEFINITION

Acenocoumarol Tablets contain Acenocoumarol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of acenocoumarol, $C_{19}H_{15}NO_6$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Heat a quantity of the powdered tablets containing 50 mg of Acenocoumarol with 30 mL of *acetone* under a reflux condenser for 5 minutes, filter and wash the residue with two 10 mL quantities of *acetone*. Evaporate the combined filtrate and washings to 5 mL, add *water* drop wise until the solution becomes turbid, heat on a water bath until the solution is clear and allow to stand. Filter, wash the crystals with a mixture of equal volumes of *acetone* and *water* and dry at 100° at a pressure of 2 kPa for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of acenocoumarol *(RS 001)*.

B. The *light absorption*, Appendix II B, of the final solution obtained in the Assay exhibits maxima at 283 nm and 306 nm.

C. Heat 25 mg of the residue obtained in test A with 2.5 mL of *glacial acetic acid*, 0.5 mL of *hydrochloric acid* and 0.2 g of *zinc powder* on a water bath for 5 minutes, cool and filter. To the filtrate add 0.05 mL of *sodium nitrite solution* and add the mixture to 10 mL of a 1% w/v solution of *2-naphthol* containing 3 mL of 5M *sodium hydroxide*. A bright red precipitate is produced.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Acenocoumarol with 5 mL of *acetone*, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 200 volumes with *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

www.webofpharma.com

https://thuocngocanh.com/

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and immediately examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 50 volumes of *chloroform* and 50 volumes of *cyclohexane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Acenocoumarol comply with the requirements stated under Tablets using the following method of analysis. Finely crush one tablet, add 30 mL of *methanol*, stir the mixture for 30 minutes and filter through sintered glass, washing the residue with three 15 mL quantities of *methanol*. To the combined filtrate and washings add 10 mL of 1M *hydrochloric acid* and sufficient *methanol* to produce 100 mL. If necessary dilute further with a solvent prepared by diluting 1 volume of 1M *hydrochloric acid* to 10 volumes with *methanol* to produce a solution containing about 0.001% w/v of Acenocoumarol. Measure the *absorbance* of the resulting solution at the maximum at 306 nm, Appendix II B. Calculate the content of $C_{19}H_{15}NO_6$ taking 521 as the value of A (1%, 1 cm) at the maximum at 306 nm.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 1 mg of Acenocoumarol add 30 mL of *methanol*, stir the mixture for 30 minutes and filter through sintered glass, washing the residue with three 15 mL quantities of *methanol*. To the combined filtrate and washings add 10 mL of 1M *hydrochloric acid* and sufficient *methanol* to produce 100 mL and measure the *absorbance* of the resulting solution at the maximum at 306 nm, Appendix II B. Calculate the content of $C_{19}H_{15}NO_6$ taking 521 as the value of A (1%, 1 cm) at the maximum at 306 nm.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

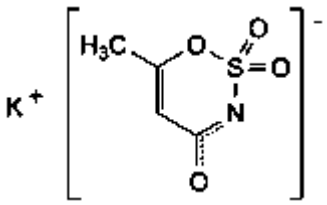
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acesulfame Potassium

General Notices

(Ph. Eur. monograph 1282)



$C_4H_4KNO_4S$ 201.2 *55589-62-3*

Action and use

Sweetening agent.

Ph Eur

DEFINITION

Potassium 6-methyl-1,2,3-oxathiazin-4-olate 2,2-dioxide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Soluble in water, very slightly soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *acesulfame potassium CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *acesulfame potassium CRS* in *water R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *acesulfame potassium CRS* and 5 mg of *saccharin sodium R* in *water R* and dilute to 5 mL with the same solvent.

Plate *cellulose for chromatography R* as the coating substance.

Mobile phase *concentrated ammonia R*, *acetone R*, *ethyl acetate R* (10:60:60 *V/V/V*).

Application 5 µL as bands.

Development Twice over 2/3 of the plate.

Drying In a current of warm air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated zones.

Results The principal zone in the chromatogram obtained with the test solution is similar in position and size to the principal zone in the chromatogram obtained with reference solution (a).

C. 0.5 mL of solution S (see Tests) gives reaction (b) of potassium (2.3.1).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 20 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

www.webofpharma.com

https://thuocngocanh.com/

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.80 g of the substance to be examined in water R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of acetylacetamide R (impurity A) in water R and dilute to 25 mL with the same solvent. To 5 mL of the solution add 45 mL of water R and dilute to 100 mL with methanol R.

Reference solution (b) To 10 mL of reference solution (a) add 1 mL of the test solution and dilute to 20 mL with methanol R.

Plate TLC silica gel plate R.

Mobile phase water R, ethanol (96 per cent) R, ethyl acetate R (2:15:74 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air until the solvents are completely removed.

Detection Spray with phosphoric vanillin solution R and heat at 120 °C for about 10 min; examine in daylight.

System suitability The chromatogram obtained with reference solution (a) shows a clearly visible spot and the chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.125 per cent).

Impurity B

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in water R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 4.0 mg of acesulfame potassium impurity B CRS in water R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 200.0 mL with water R.

Reference solution (b) Dissolve 0.100 g of the substance to be examined in reference solution (a) and dilute to 10.0 mL with the same solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (3 µm).

Mobile phase Mix 40 volumes of acetonitrile R and 60 volumes of a 3.3 g/L solution of tetrabutylammonium hydrogen sulfate R.

www.webofpharma.com

https://nhathuocngocanh.com/

Flow rate 1 mL/min.

Detection Spectrophotometer at 234 nm.

Injection 20 µL.

Run time Twice the retention time of acesulfame.

Relative retention With reference to acesulfame (retention time = about 5.3 min): impurity B = about 1.6.

System suitability:

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity B in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to acesulfame, in the chromatogram obtained with reference solution (b).

Limit:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (20 ppm).

Fluorides

Maximum 3 ppm.

Potentiometry (*2.2.36, Method I*).

Test solution Dissolve 3.000 g of the substance to be examined in *distilled water R*, add 15.0 mL of *total-ionic-strength-adjustment buffer R1* and dilute to 50.0 mL with *distilled water R*.

Reference solutions To 0.5 mL, 1.0 mL, 1.5 mL and 3.0 mL of *fluoride standard solution (10 ppm F) R* add 15.0 mL of *total-ionic-strength-adjustment buffer R1* and dilute to 50.0 mL with *distilled water R*.

Indicator electrode Fluoride-selective.

Reference electrode Silver-silver chloride.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

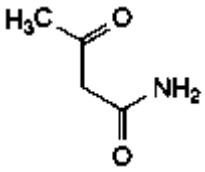
1 mL of *0.1 M perchloric acid* is equivalent to 20.12 mg of $C_4H_4KNO_4S$.

www.webofpharma.com

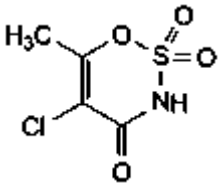
https://thuocngocanh.com/

IMPURITIES

Specified impurities *A, B.*



A. 3-oxobutanamide (acetylacetamide),



B. 5-chloro-6-methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

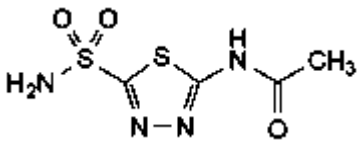
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetazolamide

General Notices

(Ph. Eur. monograph 0454)



$C_4H_6N_4O_3S_2$ 222.2 *59-66-5*

Action and use

Carbonic anhydrase inhibitor; diuretic; treatment of glaucoma and ocular hypertension; treatment of mountain sickness.

Preparation

Acetazolamide Tablets

Ph Eur

DEFINITION

N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Solution A Dissolve 30.0 mg in *0.01 M sodium hydroxide* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *0.01 M sodium hydroxide*.

Solution B Dilute 25.0 mL of solution A to 100.0 mL with *0.01 M sodium hydroxide*.

Spectral range 230-260 nm for solution A; 260-350 nm for solution B.

Absorption maximum At 240 nm for solution A; at 292 nm for solution B.

Specific absorbance at the absorption maximum 162 to 176 for solution A; 570 to 620 for solution B.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *acetazolamide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *ethanol (96 per cent) R*, evaporate to dryness and record new spectra using the residues.

C. Introduce about 20 mg into a test-tube and add 4 mL of *dilute hydrochloric acid R* and 0.2 g of *zinc powder R*. Immediately place a piece of *lead acetate paper R* over the mouth of the tube. The paper shows a brownish-black colour.

D. Dissolve about 25 mg in a mixture of 0.1 mL of *dilute sodium hydroxide solution R* and 5 mL of *water R*. Add 0.1 mL of *copper sulfate solution R*. A greenish-blue precipitate is formed.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution Y_5 or BY_5 (*2.2.2, Method II*).

Dissolve 1.0 g in 10 mL of *1 M sodium hydroxide*.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 40 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve the contents of a vial of *acetazolamide for system suitability CRS* (containing impurities A, B, C, D, E and F) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped propoxybenzene silica gel for chromatography R* (4 µm).

Mobile phase *acetonitrile for chromatography R*, 6.8 g/L solution of *potassium dihydrogen phosphate R* (10:90 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 25 µl.

Run time 3.5 times the retention time of acetazolamide.

Identification of impurities Use the chromatogram supplied with *acetazolamide for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention With reference to acetazolamide (retention time = about 8 min): impurity E = about 0.3; impurity D = about 0.4; impurity B = about 0.6; impurity C = about 1.4; impurity A = about 2.1; impurity F = about 2.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities E and D.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 2.3; impurity C = 2.6; impurity D = 1.6;

— *impurities A, B, C, D, E, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulfates (*2.4.13*)

Maximum 500 ppm.

To 0.4 g add 20 mL of *distilled water R* and dissolve by heating to boiling. Allow to cool with frequent shaking and filter.

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

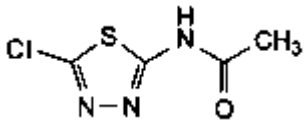
Dissolve 0.200 g in 25 mL of *dimethylformamide R*. Titrate with *0.1 M ethanolic sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 22.22 mg of $C_4H_6N_4O_3S_2$.

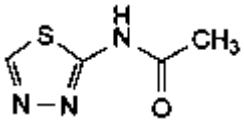
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

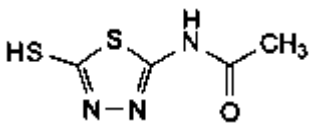
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G.*



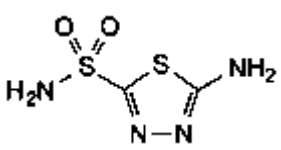
A. *N*-(5-chloro-1,3,4-thiadiazol-2-yl)acetamide,



B. *N*-(1,3,4-thiadiazol-2-yl)acetamide,



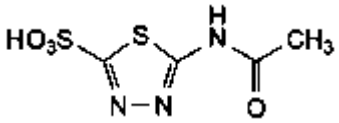
C. *N*-(5-sulfanyl-1,3,4-thiadiazol-2-yl)acetamide,



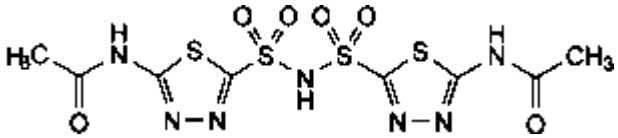
www.webofpharma.com

https://thuocngocanh.com/

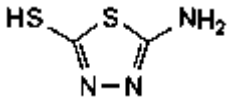
D. 5-amino-1,3,4-thiadiazole-2-sulfonamide,



E. 5-acetamido-1,3,4-thiadiazole-2-sulfonic acid,



F. *N*-[5-[(5-acetamido-1,3,4-thiadiazol-2-yl)sulfonyl]sulfamoyl-1,3,4-thiadiazol-2-yl]acetamide,



G. 5-amino-1,3,4-thiadiazole-2-thiol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetazolamide Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Carbonic anhydrase inhibitor; diuretic; treatment of glaucoma and ocular hypertension; treatment of mountain sickness.

DEFINITION

Acetazolamide Oral Suspension is a suspension containing Acetazolamide in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of acetazolamide, $C_4H_6N_4O_3S_2$

95.0 to 105.0% of the stated amount.

Shake the oral suspension vigorously before carrying out the following tests.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. To a quantity of the oral suspension containing 25 mg of Acetazolamide add 5 mL of *water*, 0.15 mL of 1M *sodium hydroxide* and 0.1 mL of *weak copper sulfate solution*. A greenish blue colour or precipitate is produced.

TESTS

Acidity

pH, 4.0 to 5.0, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions, using 900 mL of 0.01M *hydrochloric acid* as the dissolution medium and rotating the paddle at 50 revolutions per minute. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of the oral suspension containing 50 mg of Acetazolamide for 20 minutes with 10 mL of a mixture of equal volumes of *ethanol (96%)* and *ethyl acetate* and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of equal volumes of *ethanol (96%)* and *ethyl acetate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below. Use the tank without lining the walls and allow to saturate for 1 hour before development.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

A freshly prepared mixture of 20 volumes of 13.5M *ammonia*, 30 volumes of *ethyl acetate* and 50 volumes of *propan-2-ol*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a weighed quantity of the oral suspension containing 0.25 g of Acetazolamide add 50 mL of *methanol* and mix with the aid of ultrasound for 5 minutes. Add sufficient 0.01M *sodium hydroxide* to produce 200 mL and mix with the aid of shaking for 15 minutes; dilute 10 mL of the resulting solution to 100 mL with *water* and filter through a 0.45-µm filter.

(2) To 0.25 g of *acetazolamide BPCRS* add 50 mL of *methanol* and mix with the aid of ultrasound for 5 minutes. Add sufficient 0.01M *sodium hydroxide* to produce 200 mL and mix with the aid of shaking for 15 minutes; dilute 10 mL of the resulting solution to 100 mL with *water* and filter through a 0.45-µm filter.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *aminopropylsilyl silica gel for chromatography* (2.7 µm) (Ascentis Express RP-Amide is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of a 0.0631% w/v solution of *ammonium formate*, adjusted to pH 3.5 with *formic acid*.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_4H_6N_4O_3S_2$, weight in volume, using the declared content of $C_4H_6N_4O_3S_2$ in *acetazolamide BPCRS*.

STORAGE

Acetazolamide Oral Suspension should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetazolamide Tablets

General Notices

Action and use

Carbonic anhydrase inhibitor; diuretic; treatment of glaucoma, ocular hypertension, mountain sickness.

DEFINITION

Acetazolamide Tablets contain Acetazolamide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of acetazolamide, $C_4H_6N_4O_3S_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Acetazolamide with 2 mL of 1M *sodium hydroxide* and filter. Neutralise the filtrate with *glacial acetic acid*, filter and dry the resulting precipitate at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of acetazolamide *(RS 002)*.

B. Triturate a quantity of the powdered tablets containing 0.5 g of Acetazolamide with a mixture of 5 mL of *water* and 1 mL of 1M *sodium hydroxide*, transfer to a test tube, add 0.2 g of *zinc powder* and 0.5 mL of *hydrochloric acid* and immediately place a piece of *lead acetate paper* over the mouth of the tube. The paper exhibits a brownish black colour.

C. To a quantity of the powdered tablets containing 25 mg of Acetazolamide add 5 mL of *water*, 0.15 mL of 1M *sodium hydroxide* and 0.1 mL of *weak copper sulfate solution*. A greenish blue colour or precipitate is produced.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Acetazolamide for 20 minutes with 10 mL of a mixture of equal volumes of *ethanol (96%)* and *ethyl acetate* and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the same solvent mixture as for solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

www.webofpharma.com

https://thuocngocanh.com/

(b) Use a mobile phase freshly prepared as described below. Use the tank without lining the walls and allow to saturate for 1 hour before development.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of 13.5M *ammonia*, 30 volumes of *ethyl acetate* and 50 volumes of *propan-2-ol*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.4 g of Acetazolamide add 90 mL of *dimethylformamide* and carry out Method II for *non-aqueous titration*, Appendix VIII A, using 0.1M *tetrabutylammonium hydroxide VS* as titrant and determining the end point potentiometrically. Each mL of 0.1M *tetrabutylammonium hydroxide VS* is equivalent to 22.22 mg of $C_4H_6N_4O_3S_2$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetic Acid (6 per cent)

General Notices

Dilute Acetic Acid

DEFINITION

Acetic Acid (6 per cent) contains not less than 5.7% and not more than 6.3% w/w of acetic acid, $C_2H_4O_2$. It may be prepared by mixing 182 g of Acetic Acid (33 per cent) with 818 g of Purified Water.

IDENTIFICATION

A. Strongly acidic.

B. When neutralised, yields the reactions characteristic of *acetates*, Appendix VI.

TESTS

Weight per mL

About 1.005 g, Appendix V G.

Chloride

Dilute 5.0 mL with sufficient *water* to produce 100 mL. 15 mL of the resulting solution complies with the *limit test for chlorides*, Appendix VII (70 ppm).

Sulfate

12.5 mL of the solution used in the test for Chloride, diluted to 15 mL with *water*, complies with the *limit test for sulfates*, Appendix VII (240 ppm).

Aldehydes

Distil 75 mL. To the first 5 mL of the distillate add 10 mL of a 5% w/v solution of *mercury(II) chloride*, make alkaline with 5M *sodium hydroxide*, allow to stand for 5 minutes and acidify with 1M *sulfuric acid*. The solution shows not more than a faint turbidity.

Formic acid and oxidisable impurities

Mix 5 mL with 6 mL of *sulfuric acid* and cool to 20°. Add 0.4 mL of 0.0167M *potassium dichromate VS*, allow to stand for 1 minute, add 25 mL of *water* and 1 mL of freshly prepared *dilute potassium iodide solution* and titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Not less than 0.2 mL of 0.1M *sodium thiosulfate VS* is required.

Readily oxidisable impurities

www.webofpharma.com

https://thuocngocanh.com/

To 25 mL add 0.2 mL of 0.02M *potassium permanganate VS* and allow to stand for 1 minute. The pink colour is not entirely discharged.

Non-volatile matter

When evaporated to dryness and dried at 105°, leaves not more than 0.01% w/w of residue.

ASSAY

Add 30 mL of *water* to 20 g in a stopper flask and titrate with *1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator.

Each mL of *1M sodium hydroxide VS* is equivalent to 60.05 mg of $C_2H_4O_2$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetic Acid (33 per cent)

General Notices

Acetic Acid

Preparation

Acetic Acid (6 per cent)

DEFINITION

Acetic Acid (33 per cent) contains not less than 32.5% and not more than 33.5% w/w of acetic acid, $C_2H_4O_2$.

CHARACTERISTICS

A clear, colourless liquid.

Miscible with *water*, with *ethanol (96%)* and with *glycerol*.

IDENTIFICATION

A. Strongly acidic, even when diluted freely.

B. When neutralised, yields the reactions characteristic of *acetates*, Appendix VI.

TESTS

Weight per mL

1.040 to 1.042 g, Appendix V G.

Chloride

Dilute 5.0 mL with sufficient *water* to produce 100 mL. 15 mL of the resulting solution complies with the *limit test for chlorides*, Appendix VII (70 ppm).

Sulfate

12.5 mL of the solution used in the test for Chloride, diluted to 15 mL with *water*, complies with the *limit test for sulfates*, Appendix VII (240 ppm).

Aldehydes

www.webofpharma.com

https://thuocngocanh.com/

Distil 15 mL. To the first 5 mL of the distillate add 10 mL of a 5% w/v solution of *mercury(II) chloride*, make alkaline with 5M *sodium hydroxide*, allow to stand for 5 minutes and make acidic with 1M *sulfuric acid*. The solution shows not more than a faint turbidity.

Formic acid and oxidisable impurities

Mix 5 mL with 6 mL of *sulfuric acid* and cool to 20°. Add 2 mL of 0.0167M *potassium dichromate VS*, allow to stand for 1 minute, add 25 mL of *water* and 1 mL of freshly prepared *dilute potassium iodide solution* and titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Not less than 1.0 mL of 0.1M *sodium thiosulfate VS* is required.

Readily oxidisable impurities

To 5.0 mL add 20 mL of *water* and 0.2 mL of 0.02M *potassium permanganate VS* and allow to stand for 1 minute. The pink colour is not entirely discharged.

Non-volatile matter

When evaporated to dryness and dried at 105°, leaves not more than 0.01% w/w of residue.

ASSAY

Weigh 5 g into a stopper flask containing 50 mL of *water* and titrate with *1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *1M sodium hydroxide VS* is equivalent to 60.05 mg of $C_2H_4O_2$.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

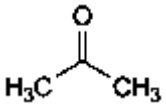
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetone

General Notices

(Ph. Eur. monograph 0872)



C_3H_6O 58.08 *67-64-1*

Ph Eur

DEFINITION

Propanone.

CHARACTERS

Appearance

Volatile, clear, colourless liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

The vapour is flammable.

IDENTIFICATION

A. Relative density (see Tests).

B. To 1 mL, add 3 mL of *dilute sodium hydroxide solution R* and 0.3 mL of a 25 g/L solution of *sodium nitroprusside R*. An intense red colour is produced which becomes violet with the addition of 3.5 mL of *acetic acid R*.

C. To 10 mL of a 0.1 per cent *V/V* solution of the substance to be examined in *ethanol (50 per cent V/V) R*, add 1 mL of a 10 g/L solution of *nitrobenzaldehyde R* in *ethanol (50 per cent V/V) R* and 0.5 mL of *strong sodium hydroxide solution R*. Allow to stand for about 2 min and acidify with *acetic acid R*. A greenish-blue colour is produced.

TESTS

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

To 10 mL add 10 mL of *water R*. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 5 mL add 5 mL of *carbon dioxide-free water R*, 0.15 mL of *phenolphthalein solution R* and 0.5 mL of *0.01 M sodium hydroxide*. The solution is pink. Add 0.7 mL of *0.01 M hydrochloric acid* and 0.05 mL of *methyl red solution R*. The solution is red or orange.

Relative density (*2.2.5*)

0.790 to 0.793.

Reducing substances

To 30 mL add 0.1 mL of *0.02 M potassium permanganate* and allow to stand in the dark for 2 h. The mixture is not completely decolourised.

Related substances

Gas chromatography (*2.2.28*).

Test solution The substance to be examined.

Reference solution (a) To 0.5 mL of *methanol R* add 0.5 mL of *2-propanol R* and dilute to 100.0 mL with the test solution. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

Reference solution (b) Dilute 100 µL of *benzene R* to 100.0 mL with the test solution. Dilute 0.20 mL of this solution to 100.0 mL with the test solution.

Column:

— *material*: fused silica,

— *size*: *l* = 50 m, Ø = 0.3 mm,

— *stationary phase*: *macrogol 20 000 R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 21 cm/s.

Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 11	45 → 100
	11 - 20	100

www.webofpharma.com

https://nhathuocngocanh.com/

	Time (min)	Temperature (°C)
Injection port		150
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Retention time Impurity C = about 7.5 min.

System suitability:

— *resolution*: minimum 5.0 between the peak due to impurity A (2nd peak) and the peak due to impurity B (3rd peak) in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 5 for the peak due to impurity C in the chromatogram obtained with reference solution (b).

Limits:

— *impurities A, B*: for each impurity, not more than the difference between the areas of the corresponding peaks in the chromatogram obtained with reference solution (a) and the areas of the corresponding peaks in the chromatogram obtained with the test solution (0.05 per cent *V/V*),

— *impurity C*: not more than the difference between the area of the peak due to impurity C in the chromatogram obtained with reference solution (b) and the area of the corresponding peak in the chromatogram obtained with the test solution (2 ppm *V/V*),

— *any other impurity*: for each impurity, not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.05 per cent *V/V*).

Matter insoluble in water

Dilute 1.0 mL to 20 mL with *water R*. The solution is clear (*2.2.1*).

Residue on evaporation

Maximum 50 ppm.

Evaporate 20.0 g to dryness on a water-bath and dry at 100-105 °C. The residue weighs a maximum of 1 mg.

Water (*2.5.12*)

Maximum 3 g/L, determined on 10.0 mL.

STORAGE

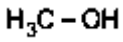
www.webofpharma.com

https://thuocngocanh.com/

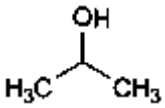
Protected from light.

IMPURITIES

Specified impurities *A, B, C.*



A. methanol,



B. propan-2-ol (isopropanol),

C. benzene.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

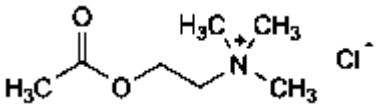
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Acetylcholine Chloride

General Notices

(Ph. Eur. monograph 1485)



$C_7H_{16}ClNO_2$ 181.7 *60-31-1*

Action and use

Cholinoceptor agonist.

Ph Eur

DEFINITION

2-(Acetyloxy)-*N*,*N*,*N*-trimethylethanaminium chloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white crystalline powder or colourless crystals, very hygroscopic.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 149 °C to 152 °C.

Introduce the substance to be examined into a capillary tube. Dry in an oven at 100-105 °C for 3 h. Seal the tube and determine the melting point.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *acetylcholine chloride CRS*.

C. Examine the chromatograms obtained in the test for related substances.

Results The principal zone in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal zone in the chromatogram obtained with reference solution (b).

D. To 15 mg add 10 mL of *dilute sodium hydroxide solution R*, 2 mL of *0.02 M potassium permanganate* and heat. The vapours formed change the colour of *red litmus paper R* to blue.

E. 0.5 mL of solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 or BY_6 (2.2.2, *Method II*).

Acidity

Dilute 1 mL of solution S to 10 mL with *carbon dioxide-free water R*. Add 0.05 mL of *phenolphthalein solution R*. Not more than 0.4 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances

Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 0.30 g of the substance to be examined in *methanol R* and dilute to 3.0 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dilute 1 mL of test solution (a) to 100 mL with *methanol R*.

Reference solution (b) Dissolve 20.0 mg of *acetylcholine chloride CRS* in *methanol R* and dilute to 2.0 mL with the same solvent.

Reference solution (c) Dissolve 20 mg of *choline chloride R* in *methanol R*, add 0.4 mL of test solution (a) and dilute to 2.0 mL with *methanol R*.

Plate *TLC silica gel plate R*.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 20 volumes of a 40 g/L solution of *ammonium nitrate R*, 20 volumes of *methanol R* and 60 volumes of *acetonitrile R*.

Application 5 µL as bands of 10 mm by 2 mm.

Development Over 2/3 of the plate.

Detection Spray with *potassium iodobismuthate solution R3*.

System suitability The chromatogram obtained with reference solution (c) shows 2 clearly separated zones.

Limits:

— *any impurity*: any zones in the chromatogram obtained with test solution (a), apart from the principal zone, are not more intense than the principal zone in the chromatogram obtained with reference solution (a) (1 per cent).

Trimethylamine

Dissolve 0.1 g in 10 mL of *sodium carbonate solution R* and heat to boiling. No vapours appear which turn *red litmus paper R* blue.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

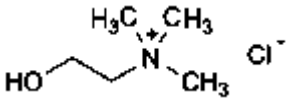
Dissolve 0.200 g in 20 mL of *carbon dioxide-free water R*. Neutralise with *0.01 M sodium hydroxide* using 0.15 mL of *phenolphthalein solution R* as indicator. Add 20.0 mL of *0.1 M sodium hydroxide* and allow to stand for 30 min. Titrate with *0.1 M hydrochloric acid*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.17 mg of $C_7H_{16}ClNO_2$.

STORAGE

In ampoules, protected from light.

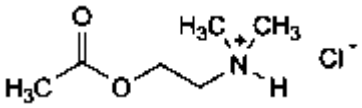
IMPURITIES



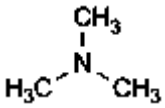
A. 2-hydroxy-*N*,*N*,*N*-trimethylethanaminium chloride (choline chloride),

www.webofpharma.com

https://thuvienthuocngocanh.com/



B. 2-(acetyloxy)-*N*,*N*-dimethylethanaminium chloride,



C. *N*,*N*-dimethylmethanamine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

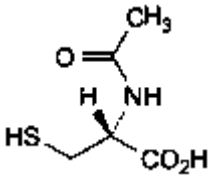
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetylcysteine

General Notices

(Ph. Eur. monograph 0967)



$C_5H_9NO_3S$ 163.2 *616-91-1*

Action and use

Sulfydryl donor; antidote to paracetamol poisoning; mucolytic.

Preparations

Acetylcysteine Eye Drops

Acetylcysteine Injection

Ph Eur

DEFINITION

(2*R*)-2-Acetamido-3-sulfanylpropanoic acid.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, C.

Second identification: B.

A. Specific optical rotation (see Tests).

B. Melting point (2.2.14).

Determination A Determine the melting point of the substance to be examined.

Result A 108 °C to 110 °C.

Determination B Mix equal parts of the substance to be examined and *acetylcysteine CRS* and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *acetylcysteine CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 21.0 to + 27.0 (dried substance).

Mix 1.25 g and 1 mL of a 10 g/L solution of *sodium edetate R*. Add 7.5 mL of a 40 g/L solution of *sodium hydroxide R*, mix and dissolve. Dilute to 25.0 mL with *phosphate buffer solution pH 7.0 R2*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solution A 1.03 g/L solution of *hydrochloric acid R*.

Test solution Suspend 0.120 g of the substance to be examined in solution A and dilute to 15.0 mL with solution A, ensuring complete dissolution.

Reference solution (a) Dilute 5.0 mL of the test solution to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (b) Dissolve 4 mg of *L-cystine R* (impurity A) in solution A and dilute to 10 mL with solution A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Dissolve 3 mg of *L-cysteine R* (impurity B), 5 mg of *acetylcysteine impurity C CRS* and 2.5 mg of *acetylcysteine impurity D CRS* in solution A, mix with 4 mL of reference solution (b) and dilute to 20 mL with solution A. Dilute 1 mL of this solution to 10 mL with the test solution.

Reference solution (d) Dissolve 2 mg of *sodium 2-methyl-2-thiazoline-4-carboxylate R* in solution A and dilute to 50 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile for chromatography R*, *water for chromatography R* previously adjusted to pH 3.0 with *phosphoric acid R* (3:97 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (a), (c) and (d).

Run time 3 times the retention time of acetylcysteine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C and D; use the chromatogram obtained with reference solution (d) to identify the peak due to 2-methyl-2-thiazoline-4-carboxylic acid.

Relative retention With reference to acetylcysteine (retention time = about 5 min): impurity A = about 0.48; impurity B = about 0.53; 2-methyl-2-thiazoline-4-carboxylic acid = about 0.8; impurity C = about 2.1; impurity D = about 2.6.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities A and B in the chromatogram obtained with reference solution (c);

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to 2-methyl-2-thiazoline-4-carboxylic acid and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to acetylcysteine in the chromatogram obtained with reference solution (c);

— *symmetry factor*: maximum 2.2 for the peak due to acetylcysteine in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 3.4; impurity C = 0.7; impurity D = 0.3;

— for each impurity, use the concentration of acetylcysteine in reference solution (a).

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity C*: maximum 0.3 per cent;

— *impurity B*: maximum 0.2 per cent;

— *impurity D*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to 2-methyl-2-thiazoline-4-carboxylic acid, which is formed due to *in situ* degradation of acetylcysteine in acidic solutions such as solution A.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Zinc

Maximum 10 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Dissolve 1.00 g in a 0.103 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Reference solutions Prepare the reference solutions using *zinc standard solution (5 mg/mL Zn) R*, diluting with a 0.103 g/L solution of *hydrochloric acid R*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame.

Use a correction procedure for non-specific absorption.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 70 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.140 g in 60 mL of *water R* and add 10 mL of *dilute hydrochloric acid R*. Add 10 mL of *potassium iodide solution R* and titrate with *0.05 M iodine*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.05 M iodine* is equivalent to 16.32 mg of $C_5H_9NO_3S$.

www.webofpharma.com

https://thuocngocanh.com/

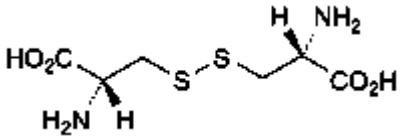
STORAGE

Protected from light.

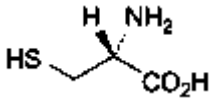
IMPURITIES

Specified impurities *B, C, D*.

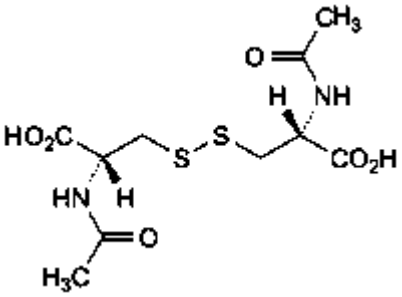
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



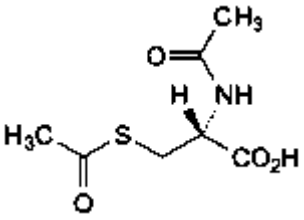
A. 3,3′-disulfanediylbis[(2*R*)-2-aminopropanoic acid] (L-cystine),



B. (2*R*)-2-amino-3-sulfanylpropanoic acid (L-cysteine),



C. 3,3′-disulfanediylbis[(2*R*)-2-acetamidopropanoic acid] (*N*,*N*′-diacetyl-L-cystine),



D. (2*R*)-2-acetamido-3-(acetylsulfanyl)propanoic acid (*N*,*S*-diacetyl-L-cysteine).

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetylcysteine Eye Drops

General Notices

Action and use

Sulfydryl donor; mucolytic; treatment of dry eye syndrome.

DEFINITION

Acetylcysteine Eye Drops are a sterile solution of Acetylcysteine in Purified Water containing Sodium Hydroxide.

The eye drops comply with the requirements stated under Eye Preparations, and with the following requirements.

Content of acetylcysteine, $C_5H_9NO_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume containing 0.8 g of Acetylcysteine add *3M hydrochloric acid* until the pH of the solution is 2.0. Add, while stirring continuously, two 200-mg portions of finely powdered *sodium chloride* followed, if necessary, by further 25-mg portions of *sodium chloride* until a precipitate begins to appear. Allow to stand for 15 minutes, filter and dry the residue at 70° at a pressure not exceeding 0.7 kPa for 2 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of acetylcysteine *(RS 003)*. Examine as discs prepared using *potassium bromide*.

TESTS

Acidity

pH, 5.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. With the exception of solution (3), the solutions should be prepared immediately before use.

(1) Dilute a volume of the eye drops with sufficient of the mobile phase to produce a solution containing 0.2% w/v of Acetylcysteine.

(2) 0.2% w/v of *acetylcysteine BPCRS* in the mobile phase.

(3) 0.2% w/v of *acetylcysteine BPCRS* in the mobile phase, stored at room temperature for at least 2 hours before use.

(4) Dissolve 20 mg of L-*cysteine* and 20 mg of L-*cystine* in 10 mL of 1M *hydrochloric acid*, add 40 mg of *acetylcysteine BPCRS* and immediately dilute to 100 mL with the mobile phase. Dilute 10 mL of the resulting solution to 200 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

(g) Inject solutions (2) and (3) and allow the chromatography to proceed for three times the retention time of acetylcysteine.

When recorded under the prescribed conditions, the chromatogram obtained with solution (4) shows three peaks with retention times of about 3.6 minutes (cystine), about 4 minutes (cysteine) and about 6 minutes (acetylcysteine).

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of a 0.5% w/v solution of *ammonium sulfate* containing 0.02M *sodium pentanesulfonate*, the solution being adjusted to pH 2.0 using 2M *hydrochloric acid*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the height of the trough separating the peaks corresponding to cysteine and cystine is less than one quarter of the height of the peak corresponding to cysteine;

in the chromatogram obtained with solution (3) a peak corresponding to *N,N′*-diacetyl-L-cystine appears which has a retention time of about 13 minutes. The area of this peak is greater than the area of any corresponding peak in the chromatogram obtained with solution (2).

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to *N,N′*-diacetyl-L-cystine is not greater than the area of the peak corresponding to acetylcysteine in the chromatogram obtained with solution (4) (1%);

the area of any peak corresponding to cysteine or cystine is not greater than the area of the corresponding peak in the chromatogram obtained with solution (4) (0.5%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the peak corresponding to acetylcysteine in the chromatogram obtained with solution (4) (1%).

Disregard any peak with an area less than 0.05 times that of the peak corresponding to acetylcysteine in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use.

(1) Dilute a volume of the eye drops with sufficient of the mobile phase to produce a solution containing 0.2% w/v of Acetylcysteine.

(2) 0.2% w/v of *acetylcysteine BPCRS* in the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_5H_9NO_3S$ in the eye drops using the declared content of $C_5H_9NO_3S$ in *acetylcysteine BPCRS*.

STORAGE

Acetylcysteine Eye Drops should be protected from light and stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include; L-cysteine, L-cystine and *N,N′*-diacetyl-L-cystine which correspond to impurities A, B and C of the European Pharmacopoeia monograph respectively.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetylcysteine Injection

General Notices

Action and use

Sulfydryl donor; antidote to paracetamol poisoning; mucolytic.

DEFINITION

Acetylcysteine Injection is a sterile solution in Water for Injections of acetylcysteine sodium, prepared by the interaction of Acetylcysteine with Sodium Hydroxide.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of acetylcysteine, $C_5H_9NO_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a volume containing the equivalent of 0.8 g of acetylcysteine add *3M hydrochloric acid* until the pH of the solution is 2. Add, while stirring continuously, two 200 mg portions of finely powdered *sodium chloride* followed, if necessary, by further 25mg portions of *sodium chloride* until a precipitate begins to appear. Allow to stand for 15 minutes, filter and dry the residue at 70° at a pressure not exceeding 0.7 kPa for 2 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of acetylcysteine *(RS 003)*. Examine as discs prepared using *potassium bromide*.

TESTS

Acidity or alkalinity

pH, 6.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. With the exception of solution (3), the solutions should be prepared immediately before use.

(1) Dilute the injection with the mobile phase to produce a solution containing the equivalent of 0.2% w/v of Acetylcysteine.

(2) 0.2% w/v solution of N-*acetyl*-L-*cysteine* in the mobile phase.

(3) 0.2% w/v solution of N-*acetyl*-L-*cysteine* in the mobile phase and store at room temperature for at least 2 hours before use.

(4) Dissolve 20 mg of L-*cysteine* and 20 mg of *L-cystine* in 10 mL of 1M *hydrochloric acid*, add 40 mg of N-*acetyl*-L-*cysteine* and immediately dilute to 100 mL with the mobile phase. Dilute 10 mL of the resulting solution to 200 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

(5) Dilute 1 volume of solution (4) to 10 volumes with mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of acetylcysteine.

The retention times of cystine, cysteine and acetylcysteine are about 3.6 minutes, 4 minutes and 6 minutes respectively.

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of a 0.5% w/v solution of *ammonium sulfate* containing 0.02M *sodium pentanesulfonate*, the mixture being adjusted to pH 2.0 using 2M *hydrochloric acid*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the height of the trough separating the peaks due to cysteine and cystine is less than one quarter of the height of the peak due to cysteine;

in the chromatogram obtained with solution (3), a peak due to *N,N'*-diacetylcystine appears which has a retention time of about 13 minutes. The area of this peak is greater than the area of any corresponding peak in the chromatogram obtained with solution (2).

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to *N,N'*-diacetylcystine is not greater than the area of the peak due to acetylcysteine in the chromatogram obtained with solution (4) (1%);

the area of any peak due to cysteine or cystine is not greater than the corresponding peak in the chromatogram obtained with solution (4) (0.5%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the peak due to acetylcysteine in the chromatogram obtained with solution (4) (1%).

Disregard any peak with an area less than the area of the peak due to acetylcysteine in the chromatogram obtained with solution (5) (0.1%).

Hydrogen sulfide

Place a quantity of the injection containing the equivalent of 0.4 g of Acetylcysteine in a round-bottomed, three-necked flask containing 40 mL of *water*. The flask is fitted with a gas inlet tube which reaches nearly to the bottom of the flask, a dropping funnel containing

www.webofpharma.com

https://thuocngocanh.com/

hydrochloric acid and an outlet tube leading to a 100 mL graduated flask containing a mixture of 1 mL of 5M *sodium hydroxide* and 50 mL of *water*. Pass through the flask a steady current of nitrogen and add 10 mL of *hydrochloric acid* from the dropping funnel. Maintain the current of nitrogen for 30 minutes and then disconnect the absorption flask. Add to the flask 10 mL of a solution prepared by dissolving 0.1 g of N,N-*dimethyl*-p-*phenylenediamine dihydrochloride* in a mixture of 45 mL of *hydrochloric acid* and 55 mL of *water* decolourised with *activated charcoal* before use, if necessary, and 5 mL of a 5% w/v solution of *iron(III) chloride hexahydrate* in 1M *hydrochloric acid* and allow to stand for 20 minutes protected from light. Add sufficient *water* to produce 100 mL and measure the *absorbance* of the solution, Appendix II B, at 665 nm using a 4 cm pathlength and using in the reference cell a solution prepared in the same manner but without the injection being examined.

Prepare a 0.4% w/v solution of *sodium sulfide*. Standardise this solution in the following manner. To 25 mL of *0.05M iodine VS* add 8 mL of *hydrochloric acid* and 25 mL of the sodium sulfide solution. Titrate with 0.1M *sodium thiosulfate solution VS* using *starch solution*, added towards the end point, as indicator. Repeat the operation without the sodium sulfide solution. The concentration of the sodium sulfide solution expressed in parts per million of hydrogen sulfide is the difference between the titrations multiplied by 68.16. Prepare a solution containing the equivalent of 20 ppm of hydrogen sulfide by appropriate dilution of the sodium sulfide solution with *water*.

Repeat the procedure carried out on the injection using 2 mL of the 20ppm hydrogen sulfide solution in place of the injection being examined. The *absorbance* of the solution obtained from the injection is not greater than the absorbance of the solution obtained from the standard (100 ppm with reference to the content of acetylcysteine).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. If necessary, dilute the injection with *water BET* to give a solution containing 10 mg per mL (solution A). The endotoxin limit concentration of solution A is not more than 0.3 IU per mL.

ASSAY

Add 20 mL of *glacial acetic acid* to a volume containing the equivalent of 0.4 g of Acetylcysteine and titrate with *0.05M iodine VS* until a permanent pale yellow colour is obtained. Each mL of *0.05M iodine VS* is equivalent to 16.23 mg of $C_5H_9NO_3S$.

STORAGE

Acetylcysteine Injection should be protected from light.

LABELLING

The strength is stated in terms of the equivalent amount of Acetylcysteine in a suitable dose-volume.

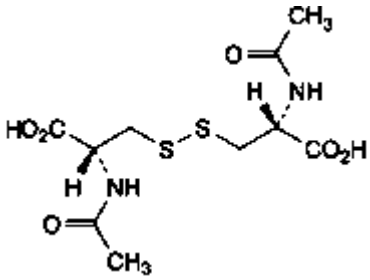
IMPURITIES

The impurities limited by the requirements of this monograph include:

1. L-cystine,
2. L-cysteine,

www.webofpharma.com

https://thuocngocanh.com/



3. *N,N′*-diacetyl-l-cystine.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

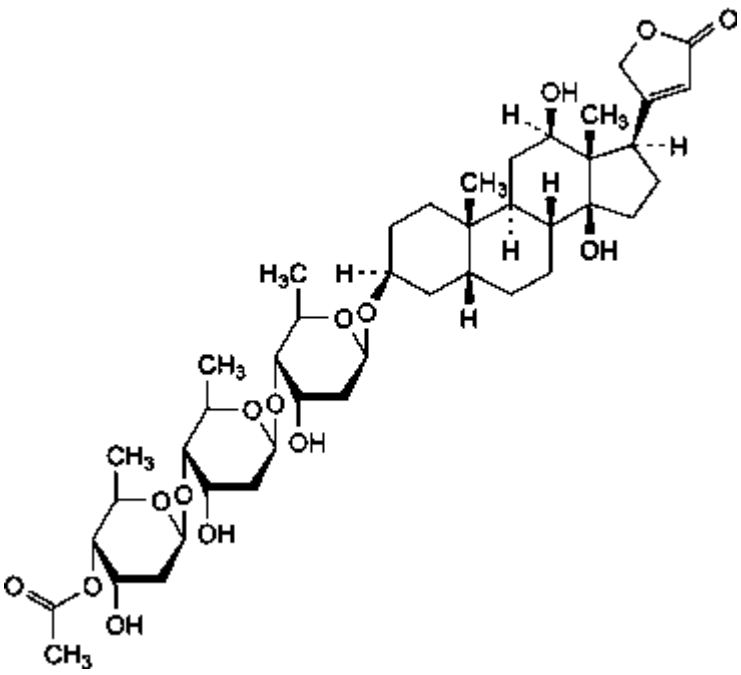
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetyldigoxin

General Notices

(β-Acetyldigoxin, Ph. Eur. monograph 2168)



$C_{43}H_{66}O_{15}$ 823 *5355-48-6*

Action and use

Cardiac Glycoside.

Ph Eur

DEFINITION

3β-[(4-*O*-Acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)- 2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *β-acetyldigoxin CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 26.2 to + 28.2 (dried substance).

Dissolve 0.50 g in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 25.0 mL with the same mixture of solvents.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture Mix equal volumes of *methanol R2* and *acetonitrile for chromatography R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 10.0 mg of *β-acetyldigoxin CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *gitoxin CRS* (impurity D) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. To 5.0 mL of this solution, add 0.5 mL of reference solution (a) and dilute to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5.0 mg of *β-acetyldigoxin for peak identification CRS* (containing impurities A and B) in 10.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	70	30
10 - 20	70 → 35	30 → 65
20 - 20.1	35 → 70	65 → 30
20.1 - 25	70	30

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatograms obtained with reference solutions (c) and (d) to identify the peaks due to impurities A, B and D.

Relative retention With reference to β-acetyldigoxin (retention time = about 9 min): impurity B = about 0.3; impurity A = about 0.7; impurity D = about 1.2.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to β-acetyldigoxin and impurity D;

— *symmetry factor*: maximum 2.5 for the peak due to β-acetyldigoxin.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity D*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *any other impurity*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *sum of impurities other than A, B and D*: not more than 1.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

www.webofpharma.com

https://thuocngocanh.com/

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Loss on drying (*2.2.32*)

Maximum 1.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{43}H_{66}O_{15}$ from the declared content of *β-acetyldigoxin CRS*.

STORAGE

Protected from light.

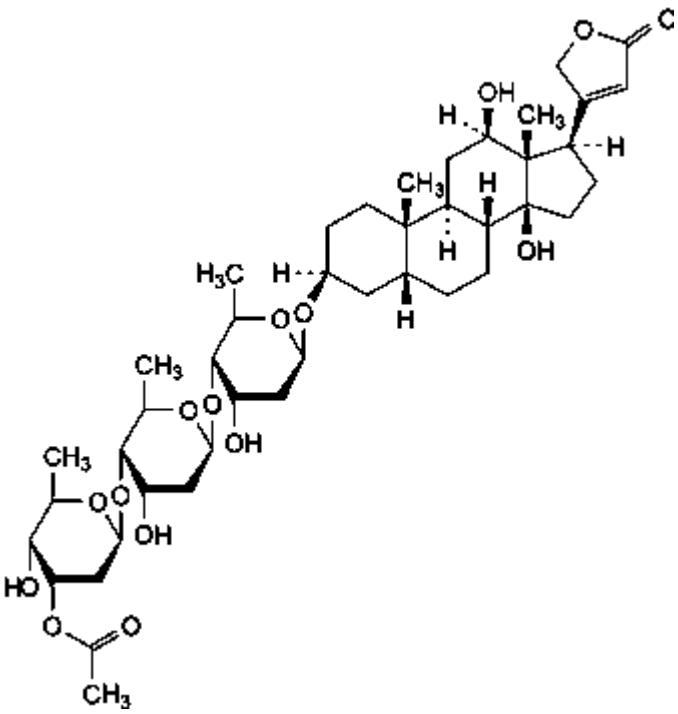
IMPURITIES

Specified impurities *A, B, D.*

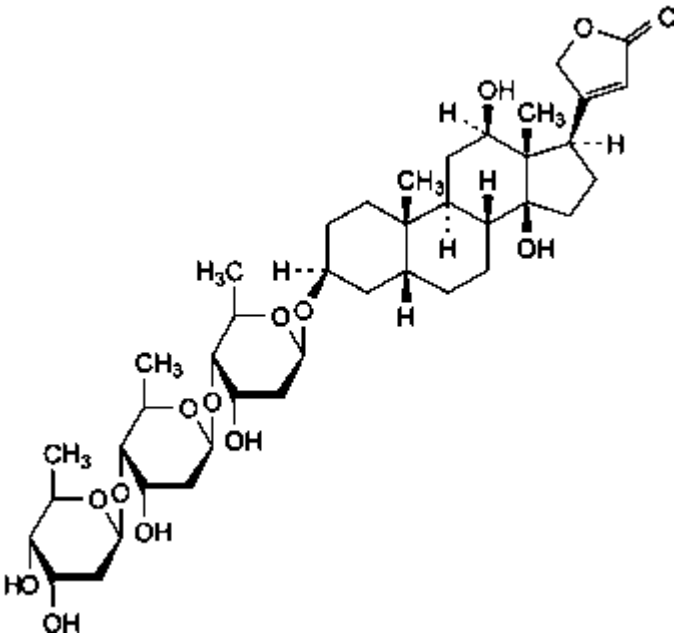
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, F, G, H.*

www.webofpharma.com

https://thuocngocanh.com/



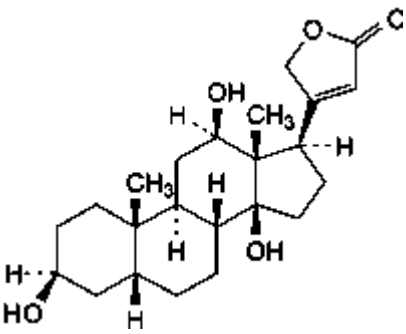
A. 3β-[(3-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (α-acetyldigoxin),



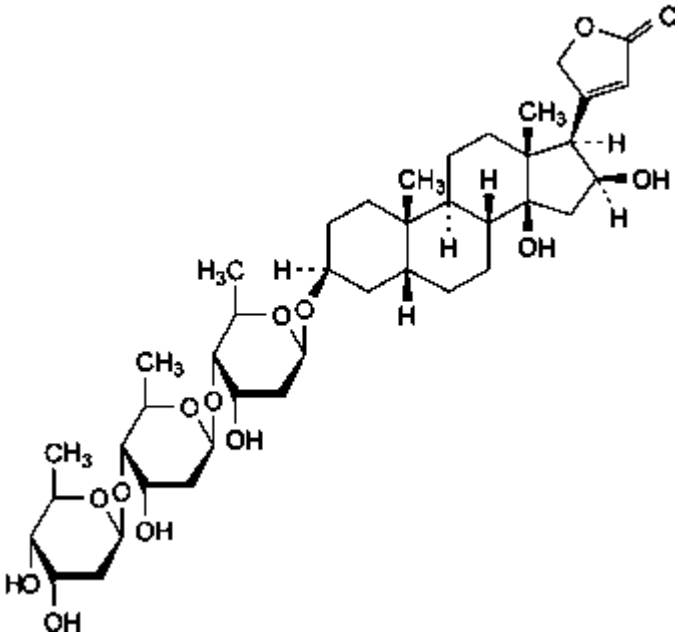
B. 3β-[(2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (digoxin),

www.webofpharma.com

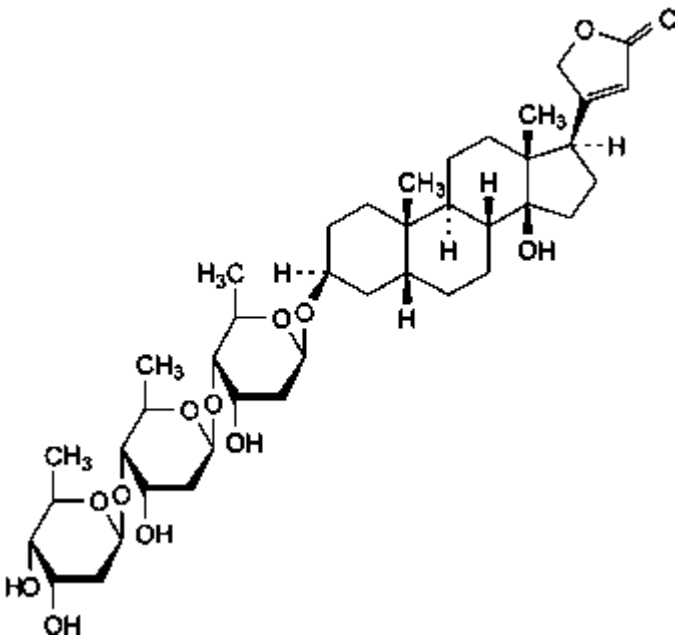
https://thuocngocanh.com/



C. 3β,12β,14-trihydroxy-5β-card-20(22)-enolide (digoxigenin),



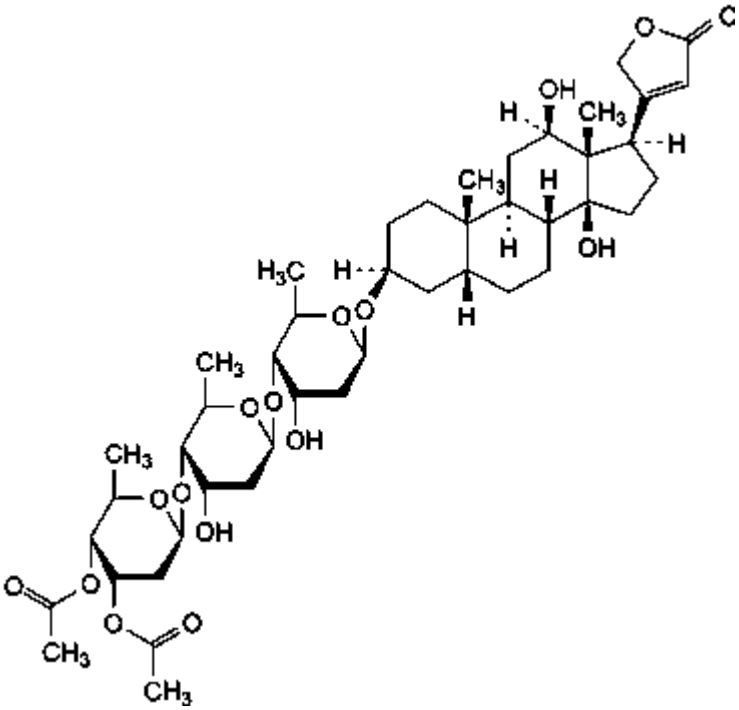
D. 3β-[(2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14,16β-dihydroxy-5β-card-20(22)-enolide (gitoxin),



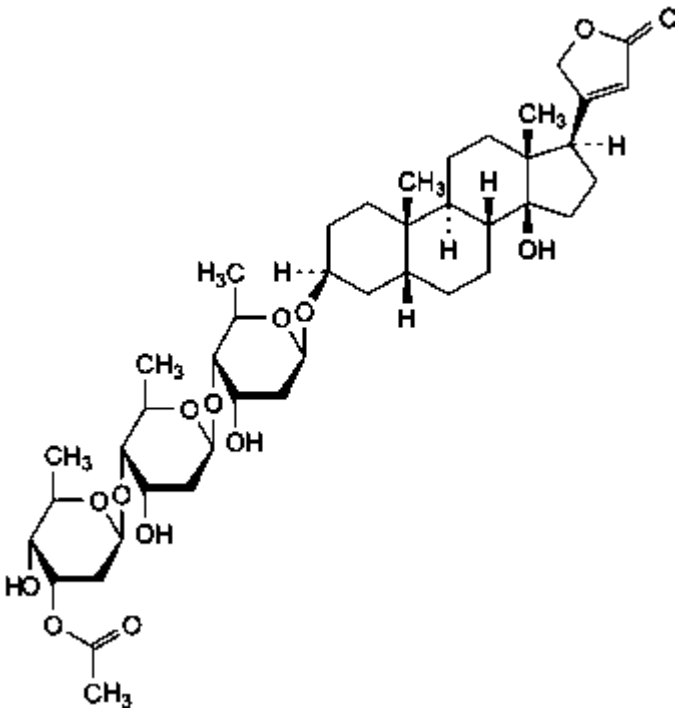
www.webofpharma.com

https://thuocngocanh.com/

E. 3β-[(2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14-hydroxy-5β-card-20(22)-enolide (digitoxin),



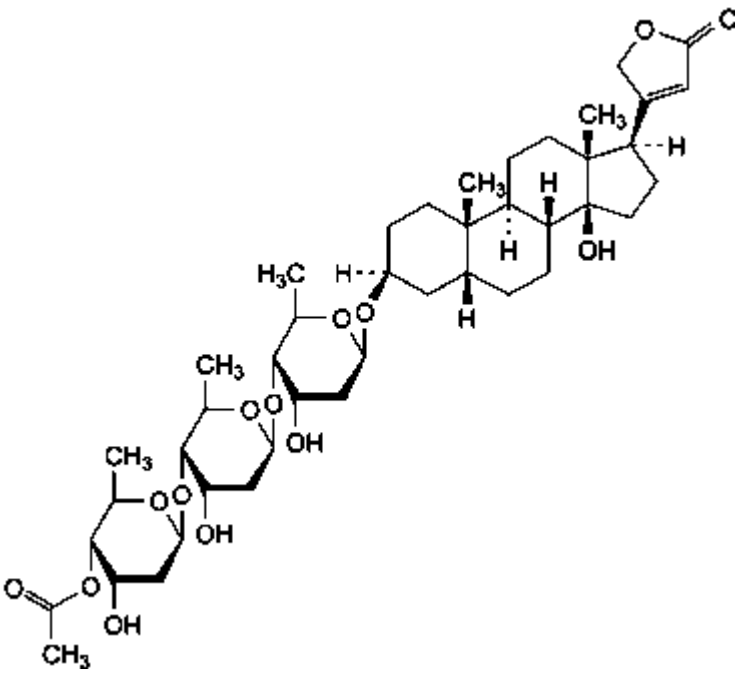
F. 3β-[(3,4-*O*-diacetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (diacetyldigoxin),



G. 3β-[(3-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14-hydroxy-5β-card-20(22)-enolide (α-acetyldigitoxin),

www.webofpharma.com

https://thuocngocanh.com/



H. 3β-[(4-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14-hydroxy-5β-card-20(22)-enolide (β-acetyldigitoxin).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetylene Intermix (1 per cent) in Nitrogen

General Notices

(Ph. Eur. monograph 2903)

Ph Eur

DEFINITION

A mixture containing 1 per cent *V/V* of acetylene in *Low-oxygen nitrogen (1685)*.

Content

0.95 per cent *V/V* to 1.05 per cent *V/V* of acetylene (C_2H_2) in nitrogen (N_2).

This monograph applies to acetylene intermix (1 per cent) in nitrogen used in the preparation of lung function test gas mixtures for medicinal use.

PRODUCTION

The acetylene used in the manufacturing process is produced by hydrolysis of calcium carbide.

Prior to using the gas in the manufacturing process, the acetylene may be passed through an activated charcoal filter.

The acetylene is stored in cylinders, which may be filled with a porous mass with acetone the only solvent permitted.

CHARACTERS

Appearance

Colourless gas.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The peak due to acetylene in the chromatogram obtained with the gas to be examined is similar in retention time and size to the peak due to acetylene in the chromatogram obtained with the reference gas.

B. Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas *Nitrogen R1*.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: *molecular sieve for chromatography R* (0.5 nm).

Carrier gas *helium for chromatography R*.

Flow rate 20 mL/min.

Temperature:

— *column*: 80 °C;

— *detector*: 130 °C.

Detection Thermal conductivity.

Injection 10 µL.

Retention time Nitrogen = about 2 min.

Results The principal peak in the chromatogram obtained with the gas to be examined is similar in retention time to the principal peak in the chromatogram obtained with the reference gas.

TESTS

Acetone

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas Mixture containing 250 ppm *V/V* of *acetone R* in *nitrogen R*.

Column:

— *material*: fused silica;

— *size*: *l* = 10 m, Ø = 0.53 mm;

— *stationary phase*: *polyorganosiloxane for oxygen-containing compounds R* (film thickness 10 µm).

Carrier gas *helium for chromatography R*.

Flow rate 50 mL/min.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

— *column*: 200 °C;

— *injection port*: 240 °C;

— *detector*: 250 °C.

Detection Flame ionisation.

Injection 25 µL.

Retention time Acetone = about 1 min.

Calculation of percentage content:

— use the concentration of acetone in the reference gas.

Limit:

— *acetone*: maximum 250 ppm *V/V*.

Arsine

Maximum 0.25 ppm *V/V*, determined using an arsine detector tube (*2.1.6*).

Phosphine

Maximum 0.2 ppm *V/V*, determined using a phosphine detector tube (*2.1.6*).

Hydrogen sulfide

Maximum 0.2 ppm *V/V*, determined using a hydrogen sulfide detector tube (*2.1.6*).

Water (*2.5.28*)

Maximum 10 ppm *V/V*.

ASSAY

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas Mixture containing 1.0 per cent *V/V* of *acetylene R* in *nitrogen R1*.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: 3 per cent *squalane R* on alumina.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Carrier gas helium for chromatography R.

Flow rate 20 mL/min.

Temperature:

— *column*: 100 °C;

— *detector*: 250 °C.

Detection Flame ionisation.

Injection 100 µL.

Retention time Acetylene = about 6 min.

Calculate the percentage content of C_2H_2.

STORAGE

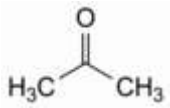
As a compressed gas, in appropriate high-pressure cylinders complying with the legal regulations.

LABELLING

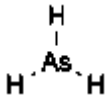
The label states the nominal content, in per cent *V/V*, of acetylene in nitrogen.

IMPURITIES

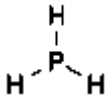
Specified impurities *A, B, C, D, E.*



A. propan-2-one (acetone),



B. arsane (arsine),



C. phosphane (phosphine),

www.webofpharma.com

https://thuvienthuocngocanh.com/

D. hydrogen sulfide,

E. water.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

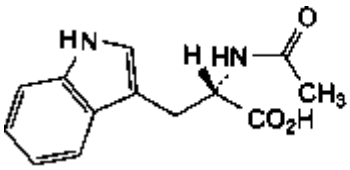
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetyltryptophan

General Notices

(N-Acetyltryptophan, Ph. Eur. monograph 1383)



and enantiomer

$C_{13}H_{14}N_2O_3$ 246.3 *87-32-1*

Ph Eur

DEFINITION

(*RS*)-2-Acetylamino-3-(1*H*-indol-3-yl)propanoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

Tryptophan used for the production of *N*-acetyltryptophan complies with the test for impurity A and other related substances in the monograph on *Tryptophan (1272)*.

CHARACTERS

Appearance

White or almost white, crystalline powder, or colourless crystals.

Solubility

Slightly soluble in water, very soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

mp

About 205 °C.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, B.

Second identification: A, C, D, E.

A. Optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *N-acetyltryptophan CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in 0.2 mL of *concentrated ammonia R* and dilute to 10 mL with *water R*.

Reference solution (a) Dissolve 50 mg of *N-acetyltryptophan CRS* in 0.2 mL of *concentrated ammonia R* and dilute to 10 mL with *water R*.

Reference solution (b) Dissolve 10 mg of *tryptophan R* in the test solution and dilute to 2 mL with the test solution.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (25:25:40 *V/V/V*).

Application 2 µL.

Development Over a path of 10 cm.

Drying In an oven at 100-105 °C for 15 min.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 2 mg in 2 mL of *water R*. Add 2 mL of *dimethylaminobenzaldehyde solution R6*. Heat on a water-bath. A blue or greenish-blue colour develops.

E. It gives the reaction of acetyl (2.3.1). Proceed as described for substances hydrolysable only with difficulty.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 or GY_7 (2.2.2, *Method II*).

Dissolve 1.0 g in a 40 g/L solution of *sodium hydroxide R* and dilute to 100 mL with the same alkaline solution.

www.webofpharma.com

https://thuocngocanh.com/

Optical rotation (2.2.7)

-0.1° to + 0.1°.

Dissolve 2.50 g in a 40 g/L solution of *sodium hydroxide R* and dilute to 25.0 mL with the same alkaline solution.

Related substances

Liquid chromatography (2.2.29). *Prepare the test and reference solutions immediately before use.*

Buffer solution pH 2.3 Dissolve 3.90 g of *sodium dihydrogen phosphate R* in 1000 mL of *water R*. Add about 700 mL of a 2.9 g/L solution of *phosphoric acid R* and adjust to pH 2.3 with the same acid solution.

Solvent mixture *acetonitrile R*, *water R* (10:90 *V/V*).

Test solution Dissolve 0.10 g of the substance to be examined in a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R* and dilute to 20.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 4.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *1,1'-ethylidenebistryptophan CRS* in 1 mL of reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, buffer solution pH 2.3 (115:885 *V/V*);

— *mobile phase B*: *acetonitrile R*, buffer solution pH 2.3 (350:650 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 45	100 → 0	0 → 100
45 - 65	0	100

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 220 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL of the test solution and reference solutions (a) and (c).

Retention time *N*-acetyltryptophan = about 29 min; 1,1′-ethylidenebis(tryptophan) = about 34 min.

System suitability Reference solution (c):

— *resolution*: minimum 8.0 between the peaks due to *N*-acetyltryptophan and 1,1′-ethylidenebis(tryptophan); if necessary, adjust the time programme for the elution gradient (an increase in the duration of elution with mobile phase A produces longer retention times and a better resolution);

— *symmetry factor*: maximum 3.5 for the peak due to 1,1′-ethylidenebistryptophan in the chromatogram obtained with reference solution (c).

Limits:

— *impurities A, B, C, D, E, F, G, H, I, J, K, L*: for each impurity, not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.01 times the area of the principal peak the chromatogram obtained with reference solution (a) (0.01 per cent).

Ammonium (*2.4.1, Method B*)

Maximum 200 ppm, determined on 0.10 g.

Prepare the standard using 0.2 mL of *ammonium standard solution (100 ppm NH_4) R*.

Iron (*2.4.9*)

Maximum 10 ppm.

Dissolve 1.0 g in 50 mL of *hydrochloric acid R1*, with heating at 50 °C. Allow to cool. In a separating funnel, shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Examine the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 5 mL of *methanol R*. Add 50 mL of *anhydrous ethanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

www.webofpharma.com

https://thuvienthuocngocanh.com/

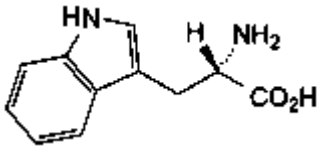
1 mL of *0.1 M sodium hydroxide* is equivalent to 24.63 mg of $C_{13}H_{14}N_2O_3$.

STORAGE

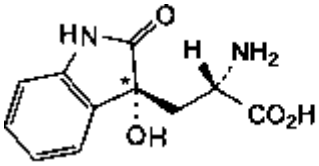
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J, K, L.*

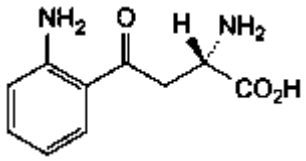


A. (*S*)-2-amino-3-(1*H*-indol-3-yl)propanoic acid (tryptophan),

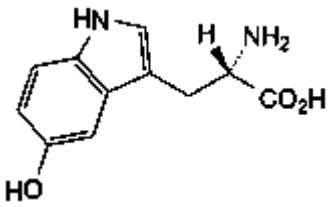


and epimer at C*

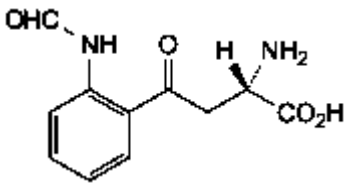
B. (*S*)-2-amino-3-[(3*RS*)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl]propanoic acid (dioxyindolylalanine),



C. (*S*)-2-amino-4-(2-aminophenyl)-4-oxobutanoic acid (kynurenine),



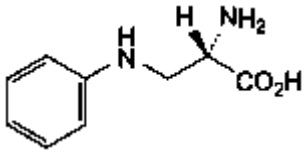
D. (*S*)-2-amino-3-(5-hydroxy-1*H*-indol-3-yl)propanoic acid (5-hydroxytryptophan),



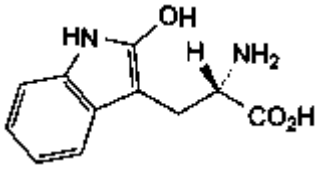
E. (*S*)-2-amino-4-[2-(formylamino)phenyl]-4-oxobutanoic acid (*N*-formylkynurenine),

www.webofpharma.com

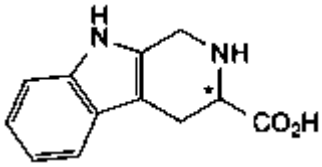
https://thuocngocanh.com/



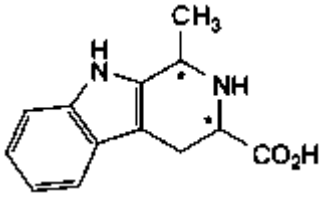
F. (*S*)-2-amino-3-(phenylamino)propanoic acid (3-phenylaminoalanine),



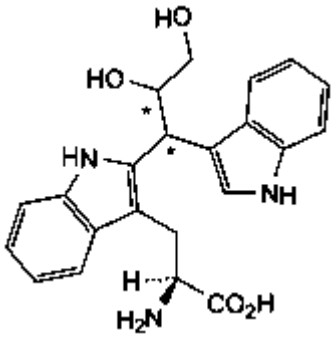
G. (*S*)-2-amino-3-(2-hydroxy-1*H*-indol-3-yl)propanoic acid (2-hydroxytryptophan),



H. (3*RS*)-1,2,3,4-tetrahydro-9*H*-β-carboline-3-carboxylic acid,



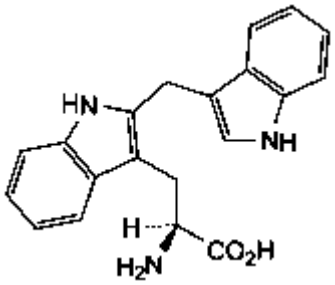
I. 1-methyl-1,2,3,4-tetrahydro-9*H*-β-carboline-3-carboxylic acid,



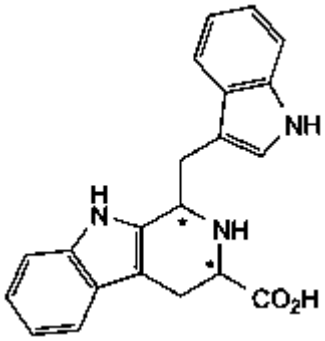
J. (*S*)-2-amino-3-[2-[2,3-dihydroxy-1-(1*H*-indol-3-yl)propyl]-1*H*-indol-3-yl]propanoic acid,

www.webofpharma.com

https://thuocngocanh.com/



K. (*S*)-2-amino-3-[2-(1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]propanoic acid,



L. 1-(1*H*-indol-3-ylmethyl)-1,2,3,4-tetrahydro-9*H*-β-carboline-3-carboxylic acid.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

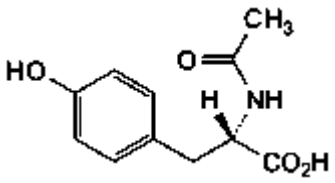
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acetyltyrosine

General Notices

(N-Acetyltyrosine, Ph. Eur. monograph 1384)



$C_{11}H_{13}NO_4$ 223.2 *537-55-3*

Ph Eur

DEFINITION

(2*S*)-2-(Acetylamino)-3-(4-hydroxyphenyl)propanoic acid.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, practically insoluble in cyclohexane.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *N-acetyltyrosine CRS*.

www.webofpharma.com

https://thuocngocanh.com/

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 80 mg of the substance to be examined in a mixture of 3 volumes of *glacial acetic acid R*, 3 volumes of *water R* and 94 volumes of *anhydrous ethanol R*, and dilute to 10 mL with the same mixture of solvents.

Reference solution Dissolve 80 mg of *N-acetyltyrosine CRS* in a mixture of 3 volumes of *glacial acetic acid R*, 3 volumes of *water R* and 94 volumes of *anhydrous ethanol R*, and dilute to 10 mL with the same mixture of solvents.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *glacial acetic acid R*, *ethyl acetate R* (10:15:75 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Solution S (see Tests) is strongly acid (2.2.4).

TESTS

Solution S

Dissolve 2.50 g in *water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

Specific optical rotation (2.2.7)

+ 46 to + 49 (dried substance).

Dilute 10.0 mL of solution S to 25.0 mL with *water R*.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 20.0 mg of *tyrosine CRS* (impurity A) in 2 mL of a 40 g/L solution of *sodium hydroxide R* and dilute to 20.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with mobile phase A.

Reference solution (d) Dilute 1.0 mL of reference solution (b) to 20.0 mL with the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 3 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 1.0 mL of *phosphoric acid R* and 1000 mL of *water for chromatography R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	97	3
2 - 15	97 → 62	3 → 38

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 219 nm.

Injection 2 µL of the test solution and reference solutions (a), (c) and (d).

Relative retention With reference to *N*-acetyltyrosine (retention time = about 6 min): impurity A = about 0.5.

System suitability Reference solution (d):

— *resolution*: minimum 5.0 between the principal peak and the peak due to impurity A.

Limits:

— *impurity A*: not more than 0.8 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.8 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: maximum 1.0 per cent;

www.webofpharma.com

https://thietbiuocngocanh.com/

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 200 ppm.

Dissolve 1.0 g in *distilled water R* and dilute to 20 mL with the same solvent.

Ammonium (2.4.1, Method B)

Maximum 200 ppm, determined on 0.100 g.

Prepare the standard using 0.2 mL of *ammonium standard solution (100 ppm NH_4) R*.

Iron (2.4.9)

Maximum 20 ppm.

In a separating funnel, dissolve 0.5 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. The aqueous layer complies with the test.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

Less than 25 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 0.180 g in 50 mL of *carbon dioxide-free water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M sodium hydroxide* is equivalent to 22.32 mg of $C_{11}H_{13}NO_4$.

STORAGE

www.webofpharma.com

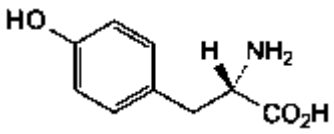
https://thuocngocanh.com/

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

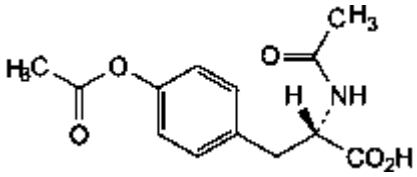
IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid (tyrosine),



B. (2*S*)-2-(acetylamino)-3-[4-(acetoxy)phenyl]propanoic acid (diacetyltyrosine).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

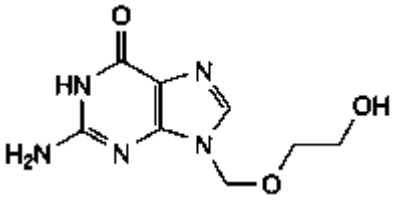
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aciclovir

General Notices

(Ph. Eur. monograph 0968)



$C_8H_{11}N_5O_3$ 225.2 *59277-89-3*

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

Preparations

Aciclovir Cream

Aciclovir Eye Ointment

Aciclovir Infusion

Aciclovir Oral Suspension

Aciclovir Tablets

Aciclovir Dispersible Tablets

Ph Eur

DEFINITION

2-Amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in heptane. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison aciclovir CRS.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, Method II).

Dissolve 0.25 g in a 4 g/L solution of sodium hydroxide R and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture dimethyl sulfoxide R, water R (20:80 *V/V*).

Phosphate buffer solution pH 2.5 Dissolve 3.48 g of dipotassium hydrogen phosphate R in 1000 mL of water for chromatography R and adjust to pH 2.5 with phosphoric acid R.

Phosphate buffer solution pH 3.1 Dissolve 3.48 g of dipotassium hydrogen phosphate R in 1000 mL of water for chromatography R and adjust to pH 3.1 with phosphoric acid R.

Test solution Dissolve 25 mg of the substance to be examined in 5.0 mL of dimethyl sulfoxide R and dilute to 25.0 mL with water R.

Reference solution (a) Dissolve 5 mg of aciclovir for system suitability A CRS (containing impurities B, J, K, N, O and P) in 1 mL of dimethyl sulfoxide R and dilute to 5 mL with water R.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of aciclovir for impurity C identification CRS in 200 µL of dimethyl sulfoxide R and dilute to 1 mL with water R.

Reference solution (d) Dissolve the contents of a vial of aciclovir for impurity G identification CRS in 1 mL of reference solution (a).

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, phosphate buffer solution pH 3.1 (1:99 *V/V*);

— *mobile phase B*: *acetonitrile R*, phosphate buffer solution pH 2.5 (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 27	100 → 80	0 → 20
27 - 40	80	20

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *aciclovir for impurity C identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity C ; use the chromatograms supplied with *aciclovir for system suitability A CRS* and *aciclovir for impurity G identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B, G, J, K, N, O and P.

Relative retention With reference to aciclovir (retention time = about 13 min): impurity B = about 0.4; impurity P = about 0.7; impurity C = about 0.9; impurity N = about 1.37; impurities O and Q = about 1.42; impurity J = about 1.62; impurities K and R = about 2.5; impurity G = about 2.6.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity C and aciclovir in the chromatogram obtained with reference solution (c); minimum 1.5 between the peaks due to impurities K and G in the chromatogram obtained with reference solution (d).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2.2;

— *impurity B*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *impurity J*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *sum of impurities K and R*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *sum of impurities O and Q*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurities C, N, P*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Water (2.5.12)

Maximum 6.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

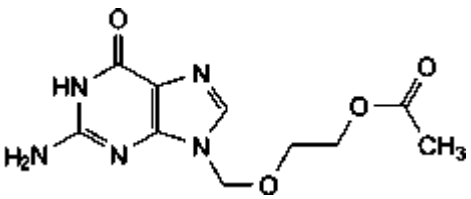
Dissolve 0.150 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 22.52 mg of $C_8H_{11}N_5O_3$.

IMPURITIES

Specified impurities *B, C, J, K, N, O, P, Q, R.*

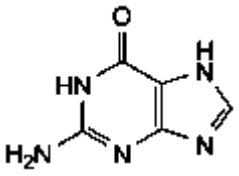
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, F, G, I, L, M.*



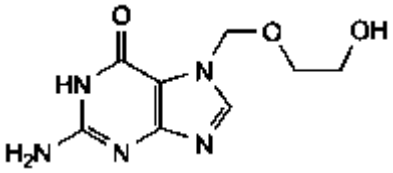
A. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl acetate,

www.webofpharma.com

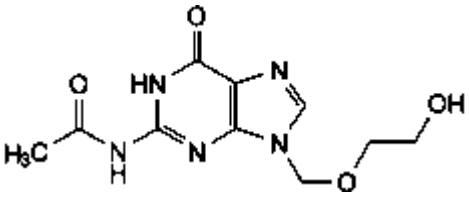
https://thuocngocanh.com/



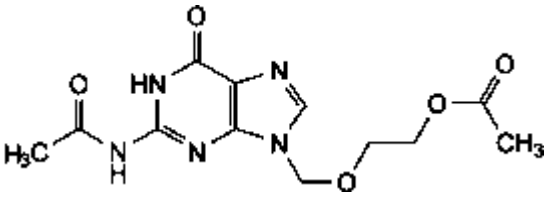
B. 2-amino-1,7-dihydro-6*H*-purin-6-one (guanine),



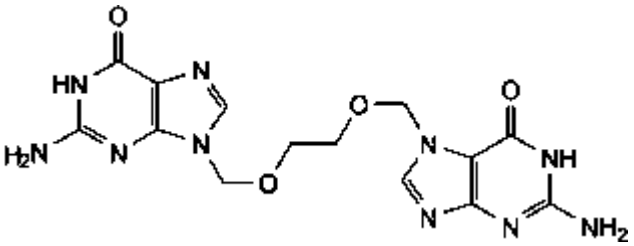
C. 2-amino-7-[(2-hydroxyethoxy)methyl]-1,7-dihydro-6*H*-purin-6-one,



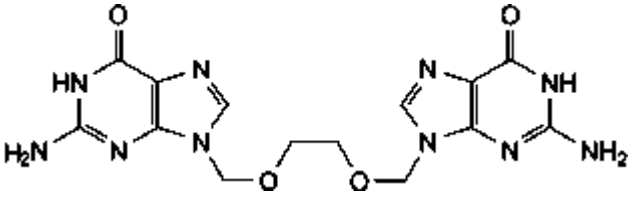
F. *N*-[9-[(2-hydroxyethoxy)methyl]-6-oxo-6,9-dihydro-1*H*-purin-2-yl]acetamide,



G. 2-[(2-acetamido-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl acetate,



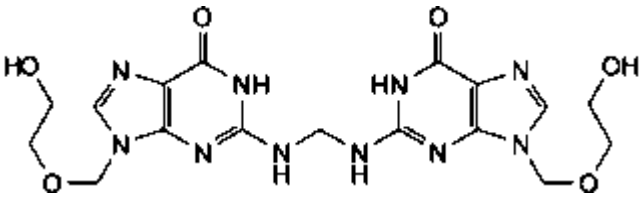
I. 2-amino-7-[[2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethoxy]methyl]-1,7-dihydro-6*H*-purin-6-one,



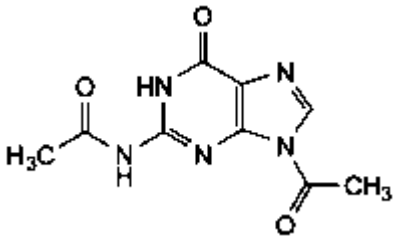
J. 9,9′-[ethane-1,2-diylbis(oxymethylene)]bis(2-amino-1,9-dihydro-6*H*-purin-6-one),

www.webofpharma.com

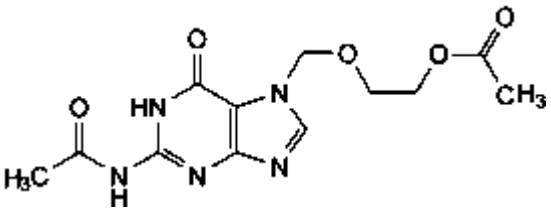
https://thuocngocanh.com/



K. 2,2′-(methylenediazanediyl)bis[9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one],



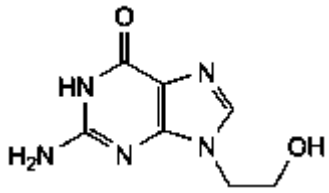
L. *N*-(9-acetyl-6-oxo-6,9-dihydro-1*H*-purin-2-yl)acetamide (N^2,9-diacetylguanine),



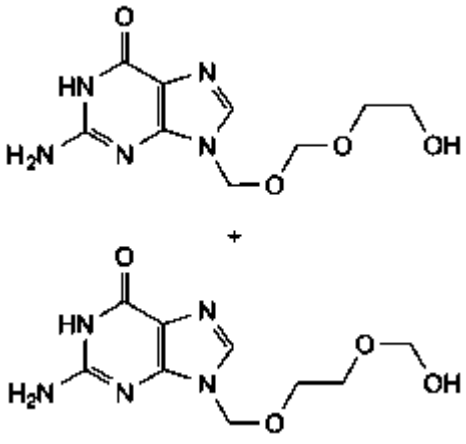
M. 2-[(2-acetamido-6-oxo-1,6-dihydro-7*H*-purin-7-yl)methoxy]ethyl acetate,

N. unknown structure,

O. unknown structure,



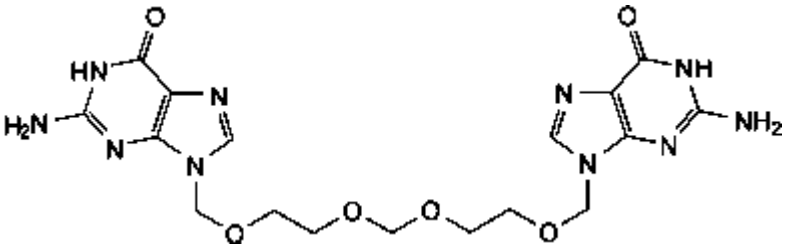
P. 2-amino-9-(2-hydroxyethyl)-1,9-dihydro-6*H*-purin-6-one,



www.webofpharma.com

https://thuocngocanh.com/

Q. mixture of 2-amino-9-[[2-(hydroxyethoxy)methoxy]methyl]-1,9-dihydro-6*H*-purin-6-one and 2-amino-9-[[2-(hydroxymethoxy)ethoxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



R. 9,9′-[methylenebis(oxyethane-2,1-diyloxymethylene)]bis(2-amino-1,9-dihydro-6*H*-purin-6-one).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aciclovir Cream

General Notices

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Aciclovir Cream contains Aciclovir in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of aciclovir, $C_8H_{11}N_5O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the well-mixed cream containing about 7.5 mg of Aciclovir with 50 mL of 0.5M *sulfuric acid*. Shake well with 50 mL of *ethyl acetate*, allow to separate and collect the clear lower aqueous layer. Wash the organic layer with 20 mL of 0.5M *sulfuric acid* and dilute the combined washings and the aqueous layer to 100 mL with 0.5M *sulfuric acid*. Mix well and filter (Whatman GF/F is suitable). Discard the first few mL of the filtrate and to 10 mL of the filtrate add sufficient *water* to produce 50 mL. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution exhibits a maximum at 255 nm and a broad shoulder at about 274 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak due to aciclovir in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Mix with the aid of ultrasound a quantity of the well-mixed cream containing 25 mg of Aciclovir in 10 mL of *dimethyl sulfoxide*, dilute to 25 mL with solution A and filter through a 0.2-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and dilute 1 volume of this solution to 5 volumes with solution A.

(3) Dissolve 5 mg of *aciclovir for system suitability A EPCRS* in 1 mL of *dimethyl sulfoxide* and dilute to 5 mL with *water*.

(4) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

(5) Dissolve the contents of a vial of *aciclovir for impurity G identification EPCRS* in 1 mL of solution (3).

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Phosphate buffer solution pH 3.1 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 3.1 with *orthophosphoric acid*.

Phosphate buffer solution pH 2.5 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 2.5 with *orthophosphoric acid*.

Mobile phase A 1 volume of *acetonitrile* and 99 volumes of phosphate buffer solution pH 3.1.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of phosphate buffer solution pH 2.5.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-27	100→80	0→20	linear gradient
27-40	80	20	isocratic
40-46	80→100	20→0	linear gradient

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity K and impurity G is at least 1.5.

LIMITS

Identify any peak in solution (1) corresponding to impurity C using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Mix with the aid of ultrasound a quantity of the well-mixed cream containing 25 mg of Aciclovir in 10 mL of *dimethyl sulfoxide*, dilute to 25 mL with solution A and filter through a 0.2-µm nylon filter. Further dilute 1 volume to 10 volumes with solution A.
(2) Dissolve 25 mg of *aciclovir BPCRS* in 10 mL of *dimethyl sulfoxide*. Dilute 2 volumes to 5 volumes with solution A and dilute 1 volume of this solution to 10 volumes with solution A.
(3) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity C and aciclovir is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}N_5O_3$ in the cream using the declared content of $C_8H_{11}N_5O_3$ in *aciclovir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aciclovir.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aciclovir Dispersible Tablets

General Notices

Dispersible Aciclovir Tablets

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Aciclovir Dispersible Tablets contain Aciclovir in a suitable dispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aciclovir, $C_8H_{11}N_5O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 0.1 g of Aciclovir add 60 mL of 0.1M *sodium hydroxide* and disperse with the aid of ultrasound for 15 minutes. Add sufficient 0.1M *sodium hydroxide* to produce 100 mL, mix well and filter. To 15 mL of the filtrate add 50 mL of *water*, 5.8 mL of 2M *hydrochloric acid* and sufficient *water* to produce 100 mL. To 5 mL of the resulting solution add sufficient 0.1M *hydrochloric acid* to produce 50 mL and mix well. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution exhibits a maximum at 255 nm and a broad shoulder at about 274 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the peak due to aciclovir in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing 25 mg of Aciclovir with 10 mL of *dimethyl sulfoxide* for 15 minutes and filter. Dilute 2 volumes of the filtrate to 5 volumes with solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and dilute 1 volume of this solution to 5 volumes with solution A.

(3) Dissolve 5 mg of *aciclovir for system suitability A EPCRS* in 1 mL of *dimethyl sulfoxide* and dilute to 5 mL with *water*.

www.webofpharma.com

https://thuocngocanh.com/

(4) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

(5) Dissolve the contents of a vial of *aciclovir for impurity G identification EPCRS* in 1 mL of solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Phosphate buffer solution pH 3.1 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 3.1 with *orthophosphoric acid*.

Phosphate buffer solution pH 2.5 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 2.5 with *orthophosphoric acid*.

Mobile phase A 1 volume of *acetonitrile* and 99 volumes of phosphate buffer solution pH 3.1.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of phosphate buffer solution pH 2.5.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-27	100→80	0→20	linear gradient
27-40	80	20	isocratic
40-46	80→100	20→0	linear gradient

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity K and impurity G is at least 1.5.

LIMITS

Identify any peak in solution (1) corresponding to impurity C using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thietbiuocngocanh.com/

the area of any peak corresponding to impurity B is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and finely powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing 25 mg of Aciclovir in 10 mL of *dimethyl sulfoxide* and filter. Dilute 2 volumes of the filtrate to 5 volumes with solution A and dilute 1 volume of this solution to 10 volumes with solution A.
(2) Dissolve 25 mg of *aciclovir BPCRS* in 10 mL of *dimethyl sulfoxide*. Dilute 2 volumes to 5 volumes with solution A and dilute 1 volume of this solution to 10 volumes with solution A.
(3) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}N_5O_3$ in the tablets using the declared content of $C_8H_{11}N_5O_3$ in *aciclovir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aciclovir.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aciclovir Eye Ointment

General Notices

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Aciclovir Eye Ointment is a sterile preparation containing Aciclovir in a suitable basis.

The eye ointment complies with the requirements stated under Eye Preparations and with the following requirements.

Content of aciclovir, $C_8H_{11}N_5O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Disperse a quantity of the eye ointment containing 10 mg of Aciclovir in 60 mL of *hexane*. Extract with three 30-mL quantities of 0.1M *sodium hydroxide*, add sufficient 0.1M *sodium hydroxide* to produce 100 mL and filter. To 15 mL of this solution add 5 mL of 2M *hydrochloric acid* and sufficient *water* to produce 100 mL. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits a maximum at 255 nm and a broad shoulder at about 274 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak due to aciclovir in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Disperse a quantity of the eye ointment containing 25 mg of Aciclovir in 10 mL of *dimethyl sulfoxide* dilute to 25 mL with solution A and filter through a 0.2-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and dilute 1 volume of this solution to 5 volumes with solution A.

(3) Dissolve 5 mg of *aciclovir for system suitability A EPCRS* in 1 mL of *dimethyl sulfoxide* and dilute to 5 mL with *water*.

(4) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

(5) Dissolve the contents of a vial of *aciclovir for impurity G identification EPCRS* in 1 mL of solution (3).

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Phosphate buffer solution pH 3.1 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 3.1 with *orthophosphoric acid*.

Phosphate buffer solution pH 2.5 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 2.5 with *orthophosphoric acid*.

Mobile phase A 1 volume of *acetonitrile* and 99 volumes of phosphate buffer solution pH 3.1.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of phosphate buffer solution pH 2.5.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-27	100→80	0→20	linear gradient
27-40	80	20	isocratic
40-46	80→100	20→0	linear gradient

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity K and impurity G is at least 1.5.

LIMITS

Identify any peak in solution (1) corresponding to impurity C using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Disperse a quantity of the eye ointment containing 25 mg of Aciclovir in 10 mL of *dimethyl sulfoxide* dilute to 25 mL with solution A and filter through a 0.2-µm nylon filter. Further dilute 1 volume to 10 volumes with solution A.
(2) Dissolve 25 mg of *aciclovir BPCRS* in 10 mL of *dimethyl sulfoxide*. Dilute 2 volumes to 5 volumes with solution A and dilute 1 volume of this solution to 10 volumes with solution A.
(3) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity C and aciclovir is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}N_5O_3$ in the eye ointment using the declared content of $C_8H_{11}N_5O_3$ in *aciclovir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aciclovir.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aciclovir Infusion

General Notices

Aciclovir Intravenous Infusion

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Aciclovir Infusion is a sterile solution containing aciclovir sodium. It is prepared by dissolving Aciclovir Sodium for Infusion with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

TESTS

Bacterial endotoxins

Carry out the test for *bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration of the infusion, diluted, if necessary, with *water BET* to give a solution containing the equivalent of 25 mg of Aciclovir per mL is 4.37 IU per mL.

STORAGE

Aciclovir Infusion should be used within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

LABELLING

The strength is stated in terms of the equivalent amount of Aciclovir in a suitable dose-volume.

ACICLOVIR SODIUM FOR INFUSION

DEFINITION

Aciclovir Sodium for Infusion is a sterile material prepared from Aciclovir with the aid of a suitable alkali. It may contain excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of aciclovir, $C_8H_{11}N_5O_3$

www.webofpharma.com

https://thuocngocanh.com/

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve the total contents of 10 containers in sufficient 0.1M *hydrochloric acid* to produce 500 mL. Dilute 3 mL of the resulting solution to 100 mL with 0.1M *hydrochloric acid* and dilute 5 mL of the resulting solution with the same solvent to produce a solution containing the equivalent of 0.0015% w/v of Aciclovir. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits a maximum at 255 nm and a broad shoulder at about 274 nm.

B. In the Assay, the retention time of the principal peak in chromatogram obtained with solution (1) is similar to that of the principal peak due to aciclovir in the chromatogram obtained with solution (2).

C. Yield reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Alkalinity

Dissolve the contents of a sealed container in sufficient *water for injections* to produce a solution containing the equivalent of 2.5% w/v of Aciclovir (solution A). The pH of solution A is 10.7 to 11.7, Appendix V L.

Clarity and colour of solution

Solution A is not more opalescent than *reference suspension II*, Appendix IV A, and not more intensely coloured than *reference solution* Y_6, Appendix IV B, Method II.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Dissolve the contents of a sealed container in sufficient *dimethyl sulfoxide* to produce a solution containing the equivalent of 2.5% w/v of Aciclovir. Dilute 1 volume of the resulting solution to 25 volumes with solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and dilute 1 volume of this solution to 5 volumes with solution A.

(3) Dissolve 5 mg of *aciclovir for system suitability A EPCRS* in 1 mL of *dimethyl sulfoxide* and dilute to 5 mL with *water*.

(4) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

(5) Dissolve the contents of a vial of *aciclovir for impurity G identification EPCRS* in 1 mL of solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Phosphate buffer solution pH 3.1 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 3.1 with *orthophosphoric acid*.

Phosphate buffer solution pH 2.5 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 2.5 with *orthophosphoric acid*.

Mobile phase A 1 volume of *acetonitrile* and 99 volumes of phosphate buffer solution pH 3.1.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of phosphate buffer solution pH 2.5.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-27	100→80	0→20	linear gradient
27-40	80	20	isocratic
40-46	80→100	20→0	linear gradient

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity K and impurity G is at least 1.5.

LIMITS

Identify any peak in solution (1) corresponding to impurity C using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B (guanine) is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Shake a quantity of the powder containing the equivalent of 25 mg of Aciclovir in 10 mL of *dimethyl sulfoxide*. Dilute 2 volumes of the filtrate to 5 volumes with solution A and dilute 1 volume of this solution to 10 volumes with solution A.
(2) Dissolve 25 mg of *aciclovir BPCRS* in 10 mL of *dimethyl sulfoxide*. Dilute 2 volumes to 5 volumes with solution A and dilute 1 volume of this solution to 10 volumes with solution A.
(3) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}N_5O_3$ in the powder using the declared content of $C_8H_{11}N_5O_3$ in *aciclovir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aciclovir.

LABELLING

The label of the sealed container states the quantity of aciclovir sodium in terms of the equivalent amount of Aciclovir.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aciclovir Oral Suspension

General Notices

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Aciclovir Oral Suspension is a suspension of Aciclovir in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of aciclovir, $C_8H_{11}N_5O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 250 nm of the solution prepared in the Assay before the final dilution exhibits a maximum at 255 nm and a broad shoulder at about 274 nm.

B. In the Related substances test, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak due to aciclovir in the chromatogram obtained with a solution prepared as follows. Dissolve 25 mg of *aciclovir BPCRS* in 10 mL of *dimethyl sulfoxide* and dilute 2 volumes of the resulting solution to 5 volumes with the solvent mixture used in the Related substances test.

TESTS

Acidity

pH, 4.0 to 7.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) To a quantity of the oral suspension containing 0.5 g of Aciclovir add 20 mL of *dimethyl sulfoxide*, shake to disperse and add sufficient solvent mixture to produce 100 mL and filter through a 0.2-µm nylon filter. Dilute 1 volume of the filtrate to 5 volumes with solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and dilute 1 volume of this solution to 5 volumes with solution A.

(3) Dissolve 5 mg of *aciclovir for system suitability A EPCRS* in 1 mL of *dimethyl sulfoxide* and dilute to 5 mL with *water*.

www.webofpharma.com

https://thuocngocanh.com/

(4) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

(5) Dissolve the contents of a vial of *aciclovir for impurity G identification EPCRS* in 1 mL of solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Phosphate buffer solution pH 3.1 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 3.1 with *orthophosphoric acid*.

Phosphate buffer solution pH 2.5 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 2.5 with *orthophosphoric acid*.

Mobile phase A 1 volume of *acetonitrile* and 99 volumes of phosphate buffer solution pH 3.1.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of phosphate buffer solution pH 2.5.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-27	100→80	0→20	linear gradient
27-40	80	20	isocratic
40-46	80→100	20→0	linear gradient

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity K and impurity G is at least 1.5.

LIMITS

Identify any peak in solution (1) corresponding to impurity C using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity B is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

To a weighed quantity containing 0.4 g of Aciclovir add 400 mL of *water* and 25 mL of 1M *sulfuric acid*, shake well, disperse with the aid of ultrasound for 10 minutes and add sufficient *water* to produce 500 mL. Filter the resulting solution, discard the first few mL of filtrate and dilute 5 mL of the filtrate to 200 mL with 0.05M *sulfuric acid*. Add 10 mL of the resulting solution to 5 mL of a 0.01% w/v solution of *cetrimide* in 0.05M *sulfuric acid*, add sufficient 0.05M *sulfuric acid* to produce 100 mL and measure the *fluorescence,* Appendix II E, using an excitation wavelength of 308 nm and an emission wavelength of 415 nm. Set the instrument to zero using a 0.0005% w/v solution of *cetrimide* in 0.05 M *sulfuric acid*. Calculate the content of $C_8H_{11}N_5O_3$ in the oral suspension from the *fluorescence* obtained by carrying out the operation at the same time using a mixture prepared by adding 10 mL of a 0.002% w/v solution of *aciclovir BPCRS* in 0.05M *sulfuric acid* and beginning at the words '… to 5 mL of a 0.01% w/v solution of *cetrimide* ...'. Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_8H_{11}N_5O_3$, weight in volume, using the declared content of $C_8H_{11}N_5O_3$ in *aciclovir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aciclovir.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aciclovir Tablets

General Notices

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Aciclovir Tablets contain Aciclovir.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aciclovir, $C_8H_{11}N_5O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 0.1 g of Aciclovir add 60 mL of 0.1M *sodium hydroxide* and disperse with the aid of ultrasound for 15 minutes. Add a sufficient quantity of 0.1M *sodium hydroxide* to produce 100 mL, mix well and filter. To 15 mL of the filtrate add 50 mL of *water* and 5.8 mL of 2M *hydrochloric acid* and sufficient *water* to produce 100 mL. To 5 mL of the solution add sufficient 0.1M *hydrochloric acid* to produce 50 mL and mix well. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution exhibits a maximum at 255 nm and a broad shoulder at about 274 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak due to aciclovir in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes, withdraw a 25 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 255 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of aciclovir, $C_8H_{11}N_5O_3$, in the medium from the absorbance obtained and taking 560 as the value of A(1%, 1 cm) at the maximum at 255 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing 25 mg of Aciclovir with 10 mL of *dimethyl sulfoxide* for 15 minutes and filter. Dilute 2 volumes of the filtrate to 5 volumes with solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and dilute 1 volume of this solution to 5 volumes with solution A.

(3) Dissolve 5 mg of *aciclovir for system suitability A EPCRS* in 1 mL of *dimethyl sulfoxide* and dilute to 5 mL with *water*.

(4) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

(5) Dissolve the contents of a vial of *aciclovir for impurity G identification EPCRS* in 1 mL of solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Phosphate buffer solution pH 3.1 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 3.1 with *orthophosphoric acid*.

Phosphate buffer solution pH 2.5 Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 2.5 with *orthophosphoric acid*.

Mobile phase A 1 volume of *acetonitrile* and 99 volumes of phosphate buffer solution pH 3.1.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of phosphate buffer solution pH 2.5.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-27	100→80	0→20	linear gradient
27-40	80	20	isocratic

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
40-46	80→100	20→0	linear gradient

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity K and impurity G is at least 1.5.

LIMITS

Identify any peak in solution (1) corresponding to impurity C using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and finely powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 1 volume of *dimethyl sulfoxide* and 4 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 25 mg of Aciclovir in 10 mL of *dimethyl sulfoxide* and filter. Dilute 2 volumes of the filtrate to 5 volumes with solution A and dilute 1 volume of this solution to 10 volumes with solution A.
(2) Dissolve 25 mg of *aciclovir BPCRS* in 10 mL of *dimethyl sulfoxide*. Dilute 2 volumes to 5 volumes with solution A and dilute 1 volume of this solution to 10 volumes with solution A.
(3) Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and aciclovir is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}N_5O_3$ in the tablets using the declared content of $C_8H_{11}N_5O_3$ in *aciclovir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aciclovir.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

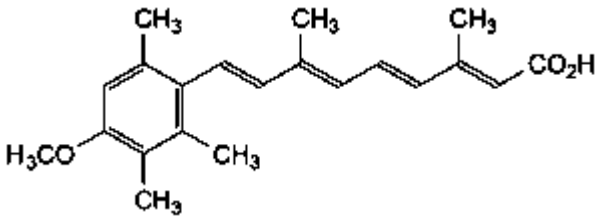
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Acitretin

General Notices

(Ph. Eur. monograph 1385)



$C_{21}H_{26}O_3$ 326.4 *55079-83-9*

Action and use

Vitamin A analogue (retinoid); treatment of psoriasis; ichthyosis; Darier's disease.

Preparation

Acitretin Capsules

Ph Eur

DEFINITION

(2*E*,4*E*,6*E*,8*E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow or greenish-yellow, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in tetrahydrofuran, slightly soluble in acetone and in ethanol (96 per cent), very slightly soluble in cyclohexane.

www.webofpharma.com

https://thuocngocanh.com/

It is sensitive to air, heat and light, especially in solution.

It shows polymorphism (5.9).

Carry out all operations as rapidly as possible and avoid exposure to actinic light; use freshly prepared solutions.

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *acitretin CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *2-propanol R* by heating under reflux; filter, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 5 mg of *acitretin CRS* in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *1,1-dimethylethyl methyl ether R*, *cyclohexane R* (2:4:40:54 *V/V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

Detection B Treat with a solution prepared as follows: dissolve 15 g of *antimony trichloride R* in 50 mL of *methylene chloride R*; examine the chromatogram in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

www.webofpharma.com

https://thietbiuocngocanh.com/

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 5 mL of *tetrahydrofuran R* and dilute to 100.0 mL with *anhydrous ethanol R*.

Test solution (b) Dilute 10.0 mL of test solution (a) to 25.0 mL with *anhydrous ethanol R*.

Reference solution (a) Dissolve 25.0 mg of *acitretin CRS* in 5 mL of *tetrahydrofuran R* and dilute to 100.0 mL with *anhydrous ethanol R*. Dilute 10.0 mL of the solution to 25.0 mL with *anhydrous ethanol R*.

Reference solution (b) Dissolve 1 mg of *tretinoin CRS* in *anhydrous ethanol R* and dilute to 20 mL with the same solvent. Mix 5 mL of the solution with 2.5 mL of reference solution (a) and dilute to 100 mL with *anhydrous ethanol R*.

Reference solution (c) Dilute 1.0 mL of the test solution (a) to 100.0 mL with *anhydrous ethanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *anhydrous ethanol R*.

Reference solution (d) Dissolve 2.5 mg of *acitretin for impurity A identification CRS* in 0.5 mL of *tetrahydrofuran R* and dilute to 10 mL with *anhydrous ethanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography for separation of polycyclic aromatic hydrocarbons R* (5 µm);

— *temperature*: 25 °C.

Mobile phase 0.3 per cent *V/V* solution of *glacial acetic acid R* in a mixture of 8 volumes of *water for chromatography R* and 92 volumes of *anhydrous ethanol R*.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 360 nm.

Autosampler Set at 4 °C.

Injection 10 µL of test solution (a) and reference solutions (b), (c) and (d).

Run time 2.5 times the retention time of acitretin.

Identification of impurities Use the chromatogram supplied with *acitretin for impurity A identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity A.

Relative retention With reference to acitretin (retention time = about 6 min): impurity A = about 0.8; tretinoin = about 0.85.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to tretinoin and acitretin.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Calculation of percentage contents:

— for each impurity, use the concentration of acitretin in reference solution (c).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 100 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{21}H_{26}O_3$ taking into account the assigned content of *acitretin CRS*.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

It is recommended that the contents of an opened container be used as soon as possible and any unused part be protected by an atmosphere of inert gas.

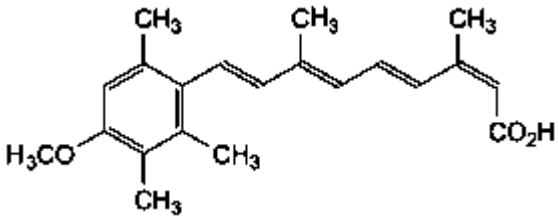
IMPURITIES

Specified impurities *A*.

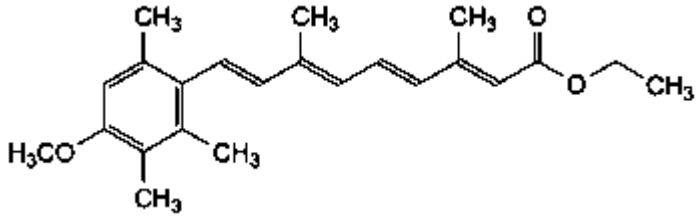
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B*.

www.webofpharma.com

https://thuocngocanh.com/



A. (2*Z*,4*E*,6*E*,8*E*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid,



B. ethyl (2*E*,4*E*,6*E*,8*E*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acitretin Capsules

General Notices

Action and use

Vitamin A analogue (retinoid); treatment of psoriasis; ichthyosis; Darier's disease.

DEFINITION

Acitretin Capsules contain Acitretin.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Carry out the following tests avoiding exposure to actinic light and using freshly prepared solutions.

Content of acitretin, $C_{21}H_{26}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the capsule contents containing 25 mg of Acitretin with sufficient *methanol* to produce 250 mL, filter and dilute 1 volume of the filtrate to 20 volumes with *methanol*. The *light absorption* spectra, Appendix II B, in the range 300 nm to 400 nm is concordant with a 0.0005% w/v solution of *acitretin BPCRS* in *methanol*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of a 3% w/v solution of *sodium lauryl sulfate* adjusted to pH 9.5 with 0.01M *hydrochloric acid* or 0.01M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a sample of the medium, filter through a 10-µm filter and measure the *absorbance* of the filtrate, suitably diluted with sufficient dissolution medium to give a solution expected to contain about 0.0005% w/v of Acitretin, at the maximum at about 348 nm, Appendix II B, using dissolution medium in the reference cell.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of acitretin, $C_{21}H_{26}O_3$, in the medium taking 1373 as the value of A(1%, 1 cm) at the maximum at 348 nm.

LIMITS

The amount of Acitretin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 10 volumes of *tetrahydrofuran* and 13 volumes of *methanol* (solvent A).

(1) Shake a quantity of the capsule contents containing 25 mg of Acitretin with 8 mL of *water* in a water bath at 45° for 10 minutes. Mix with the aid of ultrasound for 15 minutes, add sufficient solvent A to produce 100 mL and mix with the aid of ultrasound for a further 5 minutes. Filter through a 0.45-µm filter (PTFE is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A. Further dilute 4 volumes of this solution to 10 volumes with solvent A.

(3) 0.00025% w/v each of *tretinoin EPCRS* and *acitretin BPCRS* in solvent A.

(4) Dilute 1 volume of solution (2) to 4 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 365 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

0.5 volume of *glacial acetic acid*, 5 volumes of *absolute ethanol*, 21 volumes of *water* and 74 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to acitretin and tretinoin is at least 3.0;

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of not more than one *secondary peak* is greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 10 volumes of *tetrahydrofuran* and 13 volumes of *methanol* (solvent A).

(1) Shake a quantity of the mixed contents of 20 capsules containing 25 mg of Acitretin with 8 mL of *water* in a water bath at 45° for 10 minutes. Mix with the aid of ultrasound for 15 minutes, add sufficient solvent A to produce 100 mL and mix with the aid of ultrasound for a further 5 minutes. Filter through a 0.45-µm filter (PTFE is suitable) and dilute 5 mL of the filtrate to 25 mL with solvent A.

(2) 0.005% w/v of *acitretin BPCRS* in solvent A.

(3) 0.00025% w/v each of *acitretin BPCRS* and *tretinoin EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to tretinoin and acitretin is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of acitretin, $C_{21}H_{26}O_3$, in the capsules using the declared content of $C_{21}H_{26}O_3$ in *acitretin BPCRS*.

STORAGE

Acitretin Capsules should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Activated Attapulgite

General Notices

Action and use

Antidiarrhoeal.

DEFINITION

Activated Attapulgite is a purified native hydrated magnesium aluminium silicate essentially consisting of the clay mineral palygorskite that has been carefully heated to increase its adsorptive capacity.

CHARACTERISTICS

A light, cream or buff, very fine powder, free or almost free from gritty particles.

IDENTIFICATION

A. Ignite 0.5 g with 2 g of *anhydrous sodium carbonate* for 20 minutes, cool and extract with 25 mL of boiling *water*. Cool, filter, wash the residue with *water* and add the washings to the filtrate. Reserve the residue for test B. Cautiously acidify the combined filtrate and washings with *hydrochloric acid*, evaporate to dryness, moisten the residue with 0.2 mL of *hydrochloric acid*, add 10 mL of *water* and stir. A white, gelatinous precipitate is produced.

B. Wash the residue reserved in test A with *water* and dissolve in 10 mL of *2M hydrochloric acid*. To 2 mL of the solution add a 10% w/v solution of *ammonium thiocyanate*. An intense red colour is produced.

C. To 2 mL of the solution obtained in test B add 1 mL of *strong sodium hydroxide solution* and filter. To the filtrate add 3 mL of *ammonium chloride solution*. A gelatinous white precipitate is produced.

D. To 2 mL of the solution obtained in test B add *ammonium chloride* and an excess of 13.5M *ammonia* and filter. To the filtrate add 0.15 mL of *magneson reagent* and an excess of 5M *sodium hydroxide*. A blue precipitate is produced.

TESTS

Acidity or alkalinity

pH of a 5% w/v suspension in *carbon dioxide-free water*, after shaking for 5 minutes, 7.0 to 9.5, Appendix V L.

Arsenic

To 0.13 g add 5 mL of *water*, 2 mL of *sulfuric acid* and 10 mL of *sulfur dioxide solution* and evaporate on a water bath until the sulfur dioxide solution is removed and the volume reduced to about 2 mL. Transfer the solution to the generator flask with the aid of 5 mL of *water*. The resulting solution complies with the *limit test for arsenic*, Appendix VII (8 ppm).

Acid-soluble matter

www.webofpharma.com

https://thuocngocanh.com/

Boil 2 g with 100 mL of 0.2M *hydrochloric acid* under a reflux condenser for 5 minutes, cool and filter. Evaporate 50 mL of the filtrate to dryness. The residue, after ignition at about 600° for 30 minutes, weighs not more than 0.25 g.

Water-soluble matter

Boil 10 g with 100 mL of *water* under a reflux condenser for 5 minutes, cool and filter. Evaporate 50 mL of the filtrate to dryness. The residue, after ignition at 600° for 30 minutes, weighs not more than 50 mg.

Adsorptive capacity

In a stoppered bottle shake 1.0 g, in *very fine powder*, with 50 mL of a 0.12% w/v solution of *methylene blue* for 5 minutes, allow to settle and centrifuge. The colour of the clear supernatant solution is not more intense than that of a 0.0012% w/v solution of *methylene blue*.

Loss on drying

When dried to constant weight at 105°, loses not more than 4.0% of its weight. Use 1 g.

Loss on ignition

When ignited at 600°, loses not more than 9.0% of its weight. Use 1 g.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Activated Charcoal

General Notices

Decolourising Charcoal

(Ph. Eur. monograph 0313)

Action and use

Adsorbent.

Ph Eur

DEFINITION

Obtained from vegetable matter by suitable carbonisation processes intended to confer a high adsorption power.

CHARACTERS

Appearance

Black, light powder free from grittiness.

Solubility

Practically insoluble in all usual solvents.

IDENTIFICATION

A. When heated to redness it burns slowly without a flame.

B. Adsorption power (see Tests).

TESTS

Solution S

To 2.0 g in a conical flask with a ground-glass neck add 50 mL of *dilute hydrochloric acid R*. Boil gently under a reflux condenser for 1 h, filter and wash the filter with *dilute hydrochloric acid R*. Evaporate the combined filtrate and washings to dryness on a water-bath, dissolve the residue in *0.1 M hydrochloric acid* and dilute to 50.0 mL with the same acid.

Acidity or alkalinity

To 2.0 g add 40 mL of *water R* and boil for 5 min. Cool, restore to the original mass with *carbon dioxide-free water R* and filter. Reject the first 20 mL of the filtrate. To 10 mL of the filtrate add 0.25 mL of *bromothymol blue solution R1* and 0.25 mL of *0.02 M sodium hydroxide*.

www.webofpharma.com

https://thuocngocanh.com/

The solution is blue. Not more than 0.75 mL of *0.02 M hydrochloric acid* is required to change the colour of the indicator to yellow.

Acid-soluble substances

Maximum 3 per cent.

To 1.0 g add 25 mL of *dilute nitric acid R* and boil for 5 min. Filter whilst hot through a sintered-glass filter (10) (*2.1.2*) and wash with 10 mL of hot *water R*. Evaporate the combined filtrate and washings to dryness on a water-bath, add to the residue 1 mL of *hydrochloric acid R*, evaporate to dryness again and dry the residue to constant mass at 100-105 °C. The residue weighs a maximum of 30 mg.

Alkali-soluble coloured substances

To 0.25 g add 10 mL of *dilute sodium hydroxide solution R* and boil for 1 min. Cool, filter and dilute the filtrate to 10 mL with *water R*. The solution is not more intensely coloured than reference solution GY_4 (*2.2.2, Method II*).

Ethanol (96 per cent) soluble substances

Maximum 0.5 per cent.

To 2.0 g add 50 mL of *ethanol (96 per cent) R* and boil under a reflux condenser for 10 min. Filter immediately, cool, and dilute to 50 mL with *ethanol (96 per cent) R*. The filtrate is not more intensely coloured than reference solution Y_6 or BY_6 (*2.2.2, Method II*). Evaporate 40 mL of the filtrate to dryness and dry to constant mass at 100-105 °C. The residue weighs a maximum of 8 mg.

Fluorescent substances

In an intermittent-extraction apparatus, treat 10.0 g with 100 mL of *cyclohexane R1* for 2 h. Collect the liquid and dilute to 100 mL with *cyclohexane R1*. Examine in ultraviolet light at 365 nm. The fluorescence of the solution is not more intense than that of a solution of 83 µg of *quinine R* in 1000 mL of *0.005 M sulfuric acid* examined under the same conditions.

Sulfides

To 1.0 g in a conical flask add 5 mL of *hydrochloric acid R1* and 20 mL of *water R*. Heat to boiling. The fumes released do not turn *lead acetate paper R* brown.

Copper

Maximum 25 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Use solution S.

Reference solutions Prepare the reference solutions using *copper standard solution (0.1 per cent Cu) R* and diluting with *0.1 M hydrochloric acid*.

Source Copper hollow-cathode lamp.

Wavelength 325.0 nm.

www.webofpharma.com

https://thuocngocanh.com/

Atomisation device Air-acetylene flame.

Lead

Maximum 10 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Use solution S.

Reference solutions Prepare the reference solutions using *lead standard solution (100 ppm Pb) R* and diluting with *0.1 M hydrochloric acid*.

Source Lead hollow-cathode lamp.

Wavelength 283.3 nm; 217.0 nm may be used depending on the apparatus.

Atomisation device Air-acetylene flame.

Zinc

Maximum 25 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Use solution S.

Reference solutions Prepare the reference solutions using *zinc standard solution (100 ppm Zn) R* and diluting with *0.1 M hydrochloric acid*.

Source Zinc hollow-cathode lamp.

Wavelength 214.0 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 15 per cent, determined on 1.00 g by drying in an oven at 120 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 5.0 per cent, determined on 1.0 g.

Adsorption power

To 0.300 g in a 100 mL ground-glass-stoppered conical flask add 25.0 mL of a freshly prepared solution of 0.5 g of *phenazone R* in 50 mL of *water R*. Shake thoroughly for 15 min. Filter and reject the first 5 mL of filtrate. To 10.0 mL of the filtrate add 1.0 g of *potassium bromide R* and 20 mL of *dilute hydrochloric acid R*. Using 0.1 mL of *methyl red solution R* as indicator, titrate with *0.0167 M potassium*

www.webofpharma.com

https://thuocngocanh.com/

bromate until the red colour is discharged. Titrate slowly (1 drop every 15 s) towards the end of the titration. Carry out a blank titration using 10.0 mL of the phenazone solution.

Calculate the quantity of phenazone adsorbed per 100 g of activated charcoal from the following expression:

$$\frac{2.353\,(a-b)}{m}$$

a	=	number of millilitres of *0.0167 M potassium bromate* used for the blank;
b	=	number of millilitres of *0.0167 M potassium bromate* used for the test;
m	=	mass in grams of the substance to be examined.

Minimum 40 g of phenazone is adsorbed per 100 g of activated charcoal, calculated with reference to the dried substance.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

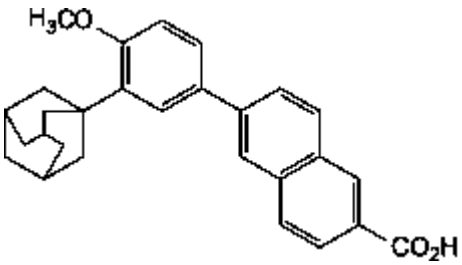
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adapalene

General Notices

(Ph. Eur. monograph 2445)



$C_{28}H_{28}O_3$ 412.5 *106685-40-9*

Action and use

Vitamin A analogue (retinoid); treatment of acne.

Preparations

Adapalene Cream

Adapalene Gel

Ph Eur

DEFINITION

6-(4-Methoxy-3-tricyclo[3.3.1.1^{3,7}]dec-1-ylphenyl)naphthalene-2-carboxylic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, sparingly soluble in tetrahydrofuran, practically insoluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison adapalene CRS.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Dissolve 0.2 g in tetrahydrofuran R and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture tetrahydrofuran R, acetonitrile R, water R (20:37:43 *V/V/V*).

Test solution (a) Dissolve 40.0 mg of the substance to be examined in 10 mL of tetrahydrofuran R, add 7 mL of the solvent mixture and dilute to 20.0 mL with tetrahydrofuran R.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in 50 mL of tetrahydrofuran R, add 35 mL of the solvent mixture and dilute to 100.0 mL with tetrahydrofuran R. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 10.0 mL with tetrahydrofuran R. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.4 mg of adapalene impurity C CRS in 2 mL of tetrahydrofuran R and dilute to 20.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with the solvent mixture. To 2.0 mL of this solution add 2.0 mL of reference solution (a) and dilute to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of adapalene for peak identification CRS (containing impurities A, C and D) in 0.5 mL of tetrahydrofuran R and dilute to 1.0 mL with the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of adapalene CRS in 50 mL of tetrahydrofuran R, add 35 mL of the solvent mixture and dilute to 100.0 mL with tetrahydrofuran R. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped phenylsilyl silica gel for chromatography R (5 µm) with a carbon loading of 7.5 per cent;

— *temperature*: 30 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: *glacial acetic acid R*, *water R* (0.1:100 *V/V*);

— *mobile phase B*: *tetrahydrofuran R*, *acetonitrile R* (35:65 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.5	50	50
2.5 - 40	50 → 28	50 → 72
40 - 42	28	72

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 25 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *adapalene for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, C and D.

Relative retention With reference to adapalene (retention time = about 20 min): impurity A = about 0.3; impurity C = about 0.9; impurity D = about 1.9.

System suitability Reference solution (b):

— *resolution*: minimum 4.5 between the peaks due to impurity C and adapalene;

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity C.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity C = 7; impurity D = 1.4;

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

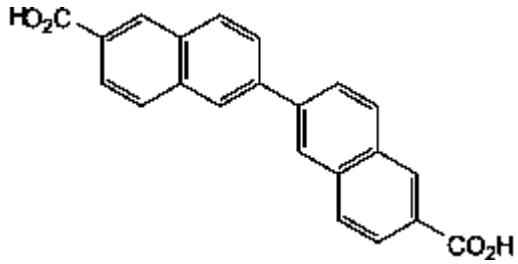
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of adapalene from the declared content of *adapalene CRS*.

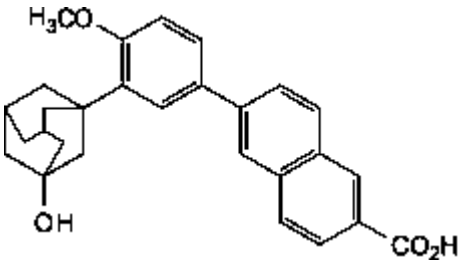
IMPURITIES

Specified impurities *A, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B.*



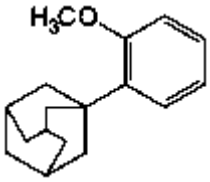
A. 2,2′-binaphthalene-6,6′-dicarboxylic acid,



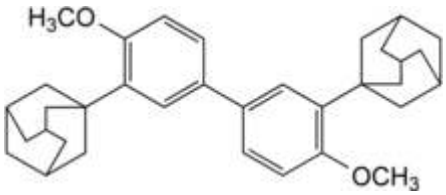
B. 6-[3-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)-4-methoxyphenyl]naphthalene-2-carboxylic acid,

www.webofpharma.com

https://thuocngocanh.com/



C. 1-(2-methoxyphenyl)tricyclo[3.3.1.1^{3,7}]decane,



D. 1,1′-[4,4′-bis(methoxy)biphenyl-3,3′-diyl]bis(tricyclo[3.3.1.1^{3,7}]decane).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adapalene Cream

General Notices

Action and use

Vitamin A analogue (retinoid); treatment of acne.

DEFINITION

Adapalene Cream contains Adapalene in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of adapalene, $C_{28}H_{28}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 10 mL of *stabiliser-free tetrahydrofuran* to a quantity of cream containing 5 mg of Adapalene and shake to disperse. Add sufficient *methanol* to produce a solution containing 0.025% w/v of Adapalene and filter (a 0.2-µm Dynagard PP filter is suitable).

(2) 0.025% w/v of *adapalene BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *octadecylsilyl silica gel F_{254}* (Merck silica gel 60 RP-18 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

18 volumes of *stabiliser-free tetrahydrofuran* and 82 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity

pH, 4.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 2 volumes of *trifluoroacetic acid* and 100 volumes of *water*.

Solvent B 10 volumes of solvent A, 25 volumes of *acetonitrile*, 30 volumes of *propan-2-ol* and 35 volumes of *stabiliser-free tetrahydrofuran*.

(1) To a quantity of the cream containing 1 mg of Adapalene, add 7 mL of *stabiliser-free tetrahydrofuran* and mix with the aid of ultrasound. Add 6 mL of *propan-2-ol*, shake, add 2 mL of solvent A and dilute to 20 mL with *acetonitrile*.

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent B.

(3) 0.005% w/v of *adapalene impurity standard BPCRS* in a mixture of equal volumes of *stabiliser-free tetrahydrofuran* and *water*.

(4) Dilute 1 volume of solution (2) to 20 volumes with solvent B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (LiChrospher 100 RP 18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a fluorimetric detector with the following programme.

Time (Minutes)	Excitation wavelength (nm)	Emission wavelength (nm)
0 - 11	260	380
11 - 30	260	347

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.2 volume of *trifluoroacetic acid* and 100 volumes of *water*.

Mobile phase B 40 volumes *stabiliser-free tetrahydrofuran* and 60 volumes of *acetonitrile*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	40→17	60→83	linear gradient
3-30	17	83	isocratic
30-31	17→40	83→60	linear gradient
31-40	40	60	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to adapalene (retention time about 6.5 minutes) are: impurity A, about 0.5 and impurity D, about 3.1.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles the chromatogram provided with *adapalene impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A or impurity D is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the impurities is not greater than 1.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent C 21 volumes of *water*, 36 volumes of *stabiliser-free tetrahydrofuran* and 43 volumes of *acetonitrile*.

(1) Disperse a quantity of the cream containing 1 mg of Adapalene in 10 mL of *stabiliser-free tetrahydrofuran* and shake with the aid of ultrasound for 5 minutes, dilute to 50 mL with solvent C and filter (a 0.2-µm Dynagard filter is suitable).
(2) Dilute 1 volume of a 0.01% w/v of *adapalene BPCRS* in *stabiliser-free tetrahydrofuran* to 5 volumes with solvent C.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) with a stainless steel pre-column (4 mm × 4 mm) both packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (LiChrospher 100 RP 18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

0.02 volume of *trifluoroacetic acid*, 21 volumes of *water*, 36 volumes of *stabiliser-free tetrahydrofuran* and 43 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency*, determined on the peak due to adapalene, is at least 4500 *theoretical plates* per metre.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{28}O_3$ in the cream using the declared content of $C_{28}H_{28}O_3$ in *adapalene BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and D listed under Adapalene.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adapalene Gel

General Notices

Action and use

Vitamin A analogue (retinoid); treatment of acne.

DEFINITION

Adapalene Gel contains Adapalene in a suitable basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of adapalene, $C_{28}H_{28}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of gel containing 5 mg of Adapalene, add 10 mL of *stabiliser-free tetrahydrofuran* and shake to disperse. Add *methanol* to produce a solution containing 0.025% w/v of Adapalene and filter (a 0.2-µm Dynagard PP filter is suitable).

(2) 0.025% w/v of *adapalene BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *octadecylsilyl silica gel F_{254}* (Merck silica gel 60 RP-18 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

18 volumes of *stabiliser-free tetrahydrofuran* and 82 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity

pH, 4.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 2 volumes of *trifluoroacetic acid* and 100 volumes of *water*.

Solvent B 10 volumes of solvent A, 25 volumes of *acetonitrile*, 30 volumes of *propan-2-ol* and 35 volumes of *stabiliser-free tetrahydrofuran*.

(1) To a quantity of the gel containing 1 mg of Adapalene add 7 mL of *stabiliser-free tetrahydrofuran* and mix with the aid of ultrasound. Add 6 mL of *propan-2-ol*, shake, add 2 mL of solvent A and dilute to 20 mL with *acetonitrile*.

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent B.

(3) 0.005% w/v of *adapalene impurity standard BPCRS* in a mixture of equal volumes of *stabiliser-free tetrahydrofuran* and *water*.

(4) Dilute 1 volume of solution (2) to 20 volumes with solvent B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (LiChrospher 100 RP 18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a fluorimetric detector with the following programme.

Time (Minutes)	Excitation wavelength (nm)	Emission wavelength (nm)
0 - 11	260	380
11 - 30	260	347

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.2 volume of *trifluoroacetic acid* and 100 volumes of *water*.

Mobile phase B 40 volumes *stabiliser-free tetrahydrofuran* and 60 volumes of *acetonitrile*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	40→17	60→83	linear gradient
3-30	17	83	isocratic
30-31	17→40	83→60	linear gradient
31-40	40	60	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to adapalene (retention time about 6.5 minutes) are: impurity A, about 0.5 and impurity D, about 3.1.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles the chromatogram provided with *adapalene impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A or impurity D is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the impurities is not greater than 1.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent C 21 volumes of *water*, 36 volumes of *stabiliser-free tetrahydrofuran* and 43 volumes of *acetonitrile*.

(1) Disperse a quantity of the gel containing 1 mg of Adapalene in 10 mL of *stabiliser-free tetrahydrofuran* and shake with the aid of ultrasound for 5 minutes, dilute to 50 mL with solvent C and filter (a 0.2-µm Dynagard PP filter is suitable).
(2) Dilute 1 volumes of a 0.01% w/v solution of *adapalene BPCRS* in *stabiliser-free tetrahydrofuran* to 5 volumes with solvent C.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) with a stainless steel pre-column (4 mm × 4 mm) both packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (LiChrospher 100 RP 18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

0.02 volume of *trifluoroacetic acid*, 21 volumes of *water*, 36 volumes of *stabiliser-free tetrahydrofuran* and 43 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency*, determined on the peak due to adapalene, is at least 4500 *theoretical plates* per metre.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{28}O_3$ in the gel using the declared content of $C_{28}H_{28}O_3$ in *adapalene BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and D listed under Adapalene.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

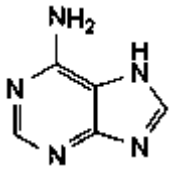
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Adenine

General Notices

(Ph. Eur. monograph 0800)



$C_5H_5N_5$ 135.1 *73-24-5*

Action and use

Constituent of anticoagulant and preservative solutions for blood.

Ph Eur

DEFINITION

Adenine contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 7*H*-purin-6-amine, calculated with reference to the dried substance.

CHARACTERS

A white or almost white powder, very slightly soluble in water and in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *adenine CRS*. Examine the substances prepared as discs.

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

C. To 1 g add 3.5 mL of *propionic anhydride R* and boil for 15 min with stirring. Cool. To the resulting crystalline mass add 15 mL of *light petroleum R* and heat to boiling with vigorous stirring. Cool and filter. Wash the precipitate with two quantities, each of 5 mL, of *light petroleum R*. Dissolve the precipitate in 10 mL of *water R* and boil for 1 min. Filter the mixture at 30 °C to 40 °C. Allow to cool. Filter, and dry the precipitate at 100 °C to 105 °C for 1 h. The melting point (*2.2.14*) of the precipitate is 237 °C to 241 °C.

TESTS

Solution S

Suspend 2.5 g in 50 mL of *distilled water R* and boil for 3 min. Cool and dilute to 50 mL with *distilled water R*. Filter. Use the filtrate as solution S.

Appearance of solution

Dissolve 0.5 g in *dilute hydrochloric acid R* and dilute to 50 mL with the same acid. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *bromothymol blue solution R1* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is blue. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is yellow.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in *dilute acetic acid R*, with heating if necessary, and dilute to 10 mL with the same acid.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *dilute acetic acid R*.

Reference solution (a) Dissolve 10 mg of *adenine CRS* in *dilute acetic acid R*, with heating if necessary, and dilute to 10 mL with the same acid.

Reference solution (b) Dilute 1 mL of test solution (b) to 20 mL with *dilute acetic acid R*.

Reference solution (c) Dissolve 10 mg of *adenine CRS* and 10 mg of *adenosine R* in *dilute acetic acid R*, with heating if necessary, and dilute to 10 mL with the same acid.

Apply to the plate 5 µL of each solution. Develop over a path of 12 cm using a mixture of 20 volumes of *concentrated ammonia R*, 40 volumes of *ethyl acetate R* and 40 volumes of *propanol R*. Dry the plate in a current of warm air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated spots.

Chlorides (*2.4.4*)

www.webofpharma.com

https://thuocngocanh.com/

To 10 mL of solution S add 1 mL of *concentrated ammonia R* and 3 mL of *silver nitrate solution R2*. Filter. Wash the precipitate with a little *water R* and dilute the filtrate to 15 mL with *water R*. The solution complies with the limit test for chlorides (100 ppm). When carrying out the test, add 2 mL of *dilute nitric acid R* instead of 1 mL of *dilute nitric acid R*.

Sulfates (*2.4.13*)

Dilute 10 mL of solution S to 15 mL with *distilled water R*. The solution complies with the limit test for sulfates (300 ppm).

Ammonium

Prepare a cell consisting of two watch-glasses 60 mm in diameter placed edge to edge. To the inner wall of the upper watch-glass stick a piece of *red litmus paper R* 5 mm square and wetted with a few drops of *water R*. Finely powder the substance to be examined, place 0.5 g in the lower watch-glass and suspend in 0.5 mL of *water R*. To the suspension add 0.30 g of *heavy magnesium oxide R*. Briefly triturate with a glass rod. Immediately close the cell by putting the two watch-glasses together. Heat at 40 °C for 15 min. The litmus paper is not more intensely blue coloured than a standard prepared at the same time and in the same manner using 0.05 mL of *ammonium standard solution (100 ppm NH_4) R*, 0.5 mL of *water R* and 0.30 g of *heavy magnesium oxide R* (10 ppm).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in a mixture of 20 mL of *acetic anhydride R* and 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 13.51 mg of $C_5H_5N_5$.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

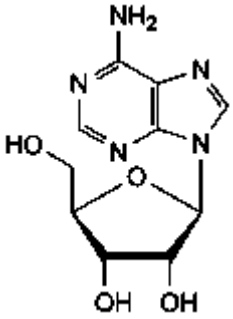
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adenosine

General Notices

(Ph. Eur. monograph 1486)



$C_{10}H_{13}N_5O_4$ 267.2 *58-61-7*

Action and use

Antiarrhythmic.

Ph Eur

DEFINITION

9-β-D-Ribofuranosyl-9*H*-purin-6-amine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, soluble in hot water, practically insoluble in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute mineral acids.

mp

Loading [MathJax]/jax/output/HTML-CSS/fonts/TeX/fontdata.js

About 234 °C.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *adenosine CRS*.

TESTS

Solution S

Suspend 5.0 g in 100 mL of *distilled water R* and heat to boiling. Allow to cool, filter with the aid of vacuum and dilute to 100 mL with *distilled water R*.

Appearance of solution

Solution S is colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S, add 0.1 mL of *bromocresol purple solution R* and 0.1 mL of *0.01 M hydrochloric acid*. The solution is yellow. Add 0.4 mL of *0.01 M sodium hydroxide*. The solution is violet-blue.

Specific optical rotation (*2.2.7*)

-45 to -49 (dried substance).

Dissolve 1.25 g in *1 M hydrochloric acid* and dilute to 50.0 mL with the same acid. Examine within 10 min of preparing the solution.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Dissolve 6.8 g of *potassium hydrogen sulfate R* and 3.4 g of *tetrabutylammonium hydrogen sulfate R* in *water R*, adjust to pH 6.5 with a 60 g/L solution of *potassium hydroxide R* and dilute to 1000 mL with the same solvent. Use a freshly prepared solvent mixture.

Test solution Dissolve 20 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *adenine R* (impurity A) and 5 mg of *inosine R* (impurity G) in the mobile phase and dilute to 50 mL with the mobile phase. Dilute 4 mL of this solution to 100 mL with the mobile phase.

Column:

Loading [MathJax]/jax/output/HTML-CSS/fonts/TeX/fontdata.js

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water R*, solvent mixture (40:60 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 1.5 times the retention time of adenosine.

Relative retention With reference to adenosine (retention time = about 13 min): impurity A = about 0.3; impurity G = about 0.4.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and G.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity G = 1.4;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm, determined on solution S.

Ammonium (*2.4.1, Method B*)

Maximum 10 ppm, determined on 0.5 g.

Prepare the standard using 5 mL of *ammonium standard solution (1 ppm NH_4) R*.

Loading [MathJax]/jax/output/HTML-CSS/fonts/TeX/fontdata.js

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

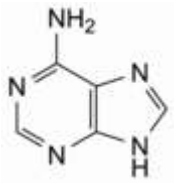
Dissolve 0.200 g, warming slightly if necessary, in a mixture of 20 mL of *acetic anhydride R* and 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 26.72 mg of $C_{10}H_{13}N_5O_4$.

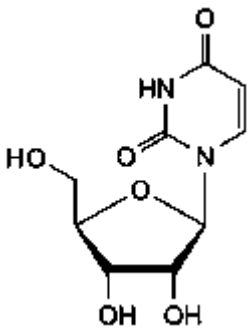
IMPURITIES

Specified impurities *A, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F, H.*



A. 7*H*-purin-6-amine (adenine),

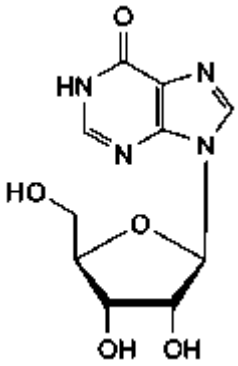


F. 1-β-D-ribofuranosylpyrimidine-2,4(1*H*,3*H*)-dione (uridine),

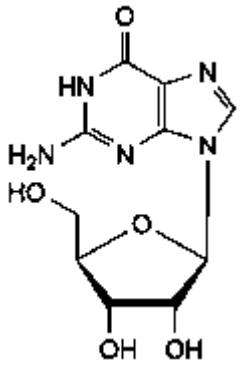
Loading [MathJax]/jax/output/HTML-CSS/fonts/TeX/fontdata.js

www.webofpharma.com

https://thuocngocanh.com/



G. 9-β-D-ribofuranosyl-1,9-dihydro-6*H*-purin-6-one (inosine),



H. 2-amino-9-β-D-ribofuranosyl-1,9-dihydro-6*H*-purin-6-one (guanosine).

Ph Eur

© Crown Copyright 2022

Loading [MathJax]/jax/output/HTML-CSS/fonts/TeX/fontdata.js

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adipic Acid

General Notices

(Ph. Eur. monograph 1586)

$C_6H_{10}O_4$ 146.1 *124-04-9*

Action and use

Excipient.

Ph Eur

DEFINITION

Hexanedioic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in boiling water, freely soluble in ethanol (96 per cent) and in methanol, soluble in acetone.

IDENTIFICATION

A. Melting point (*2.2.14*): 151 °C to 154 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *adipic acid CRS*.

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 5.0 g with heating in *distilled water R* and dilute to 50 mL with the same solvent. Allow to cool and to crystallise. Filter through a sintered-glass filter (40) (2.1.2). Wash the filter with *distilled water R*. Collect the filtrate and the washings until a volume of 50 mL is obtained.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 1.0 g in *methanol R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.20 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 20 mg of *glutaric acid R* in 1.0 mL of the test solution and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase, dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm,

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 350 m^2/g and a pore size of 10 nm,

— *temperature*: 30 °C.

Mobile phase Mix 3 volumes of *acetonitrile R* and 97 volumes of a 24.5 g/L solution of *dilute phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 209 nm.

Injection 20 µL.

Run time 3 times the retention time of adipic acid.

System suitability Reference solution (a):

— *resolution*: minimum 9.0 between the peaks due to glutaric acid and adipic acid.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Nitrates

Maximum 30 ppm.

To 1 mL of solution S add 2 mL of *concentrated ammonia R*, 0.5 mL of a 10 g/L solution of manganese sulfate R, 1 mL of a 10 g/L solution of *sulfanilamide R* and dilute to 20 mL with *water R*. Add 0.10 g of *zinc powder R* and cool in iced water for 30 min; shake from time to time. Filter and cool 10 mL of the filtrate in iced water. Add 2.5 mL of *hydrochloric acid R1* and 1 mL of a 10 g/L solution of *naphthylethylenediamine dihydrochloride R*. Allow to stand at room temperature. After 15 min the mixture is not more intensely coloured than a standard prepared at the same time and in the same manner, using 1.5 mL of *nitrate standard solution (2 ppm NO_3) R* instead of 1 mL of solution S. The test is invalid if a blank solution prepared at the same time and in the same manner, using 1 mL of *water R* instead of 1 mL of solution S, is more intensely coloured than a 2 mg/L solution of *potassium permanganate R*.

Sulfates (2.4.13)

Maximum 500 ppm.

Dilute 3 mL of solution S to 15 mL with *distilled water R*.

Iron (2.4.9)

Maximum 10 ppm, determined on solution S.

Loss on drying (2.2.32)

Maximum 0.2 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent.

Melt 1.0 g completely over a gas burner, then ignite the melted substance with the burner. After ignition, lower or remove the flame in order to prevent the substance from boiling and keep it burning until completely carbonised. Carry out the test for sulfated ash using the residue.

ASSAY

Dissolve 60.0 mg in 50 mL of *water R*. Add 0.2 mL of *phenolphthalein solution R* and titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 7.31 mg of $C_6H_{10}O_4$.

IMPURITIES

www.webofpharma.com

https://thuocngocanh.com/

A. pentanedioic acid (glutaric acid),

B. butanedioic acid (succinic acid),

C. heptanedioic acid (pimelic acid).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

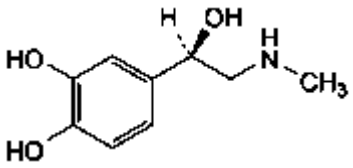
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Adrenaline / Epinephrine

General Notices

(Ph. Eur. monograph 2303)



$C_9H_{13}NO_3$ 183.2 *51-43-4*

Action and use

Adrenoceptor agonist.

Preparations

Adrenaline Eye Drops/Epinephrine Eye Drops

Dilute Adrenaline Injection (1 in 10,000)/Dilute Epinephrine Injection (1 in 10,000)

Ph Eur

DEFINITION

4-[(1*R*)-1-Hydroxy-2-(methylamino)ethyl]benzene-1,2-diol.

Synthetic product.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white crystalline powder, becoming coloured on exposure to air and light.

Solubility

www.webofpharma.com

https://thuvienthuocngocanh.com/

Practically insoluble in water, in ethanol (96 per cent) and in methylene chloride. It dissolves in hydrochloric acid.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison adrenaline CRS.

B. Specific optical rotation (see Tests).

TESTS

Solution S

Dissolve 1.000 g in a 25.75 g/L solution of hydrochloric acid R and dilute to 50.0 mL with the same solvent. Examine the solution immediately.

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, Method II).

Specific optical rotation (2.2.7)

-54.0 to -50.0 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions protected from light.*

Solvent mixture A Dissolve 5.0 g of potassium dihydrogen phosphate R and 2.6 g of sodium octanesulfonate R in water for chromatography R and dilute to 1000 mL with the same solvent (it is usually necessary to stir for at least 30 min to achieve complete dissolution). Adjust to pH 2.8 with phosphoric acid R.

Solvent mixture B acetonitrile R, solvent mixture A (13:87 *V/V*).

Solvent mixture C 10.3 g/L solution of hydrochloric acid R, solvent mixture B (10:90 *V/V*).

Test solution Dissolve 40.0 mg of the substance to be examined in 5 mL of a 10.3 g/L solution of hydrochloric acid R and dilute to 50.0 mL with solvent mixture B.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solvent mixture B. Dilute 1.0 mL of this solution to 10.0 mL with solvent mixture B.

Reference solution (b) Dissolve 1.5 mg of noradrenaline tartrate CRS (impurity B) and 1.5 mg of adrenalone hydrochloride R (impurity C) in solvent mixture B, add 1 mL of the test solution and dilute to 100 mL with solvent mixture B.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Dissolve the contents of a vial of *adrenaline impurity mixture CRS* (containing impurities D and E) in 1 mL of solvent mixture C.

Reference solution (d) Dissolve the contents of a vial of *adrenaline impurity F CRS* in 1 mL of a 10.3 g/L solution of *hydrochloric acid R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, solvent mixture A (5:95 *V/V*);

— *mobile phase B*: *acetonitrile R1*, solvent mixture A (45:55 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	92 → 50	8 → 50
15 - 20	50 → 92	50 → 8
20 - 25	92	8

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C; use the chromatogram supplied with *adrenaline impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to adrenaline (retention time = about 4 min): impurity F = about 0.2; impurity B = about 0.8; impurity C = about 1.3; impurity D = about 3.3; impurity E = about 3.7.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurity B and adrenaline.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.7; impurity E = 0.6;

www.webofpharma.com

https://thuocngocanh.com/

— *impurities B, C, F*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.32)

Maximum 0.4 per cent, determined on 0.300 g using the evaporation technique at 130 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

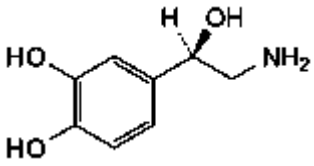
1 mL of *0.1 M perchloric acid* is equivalent to 18.32 mg of $C_9H_{13}NO_3$.

STORAGE

Under nitrogen, protected from light.

IMPURITIES

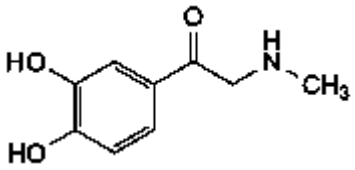
Specified impurities *B, C, D, E, F*.



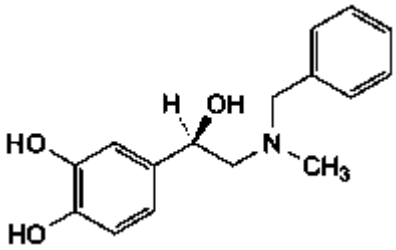
B. 4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol (noradrenaline),

www.webofpharma.com

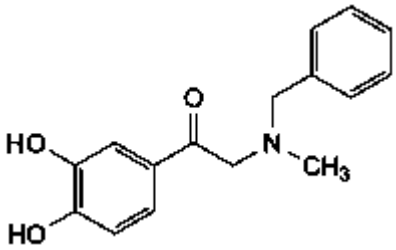
https://thuocngocanh.com/



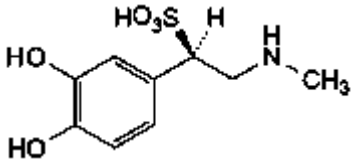
C. 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethan-1-one (adrenalone),



D. 4-[(1*R*)-2-[benzyl(methyl)amino]-1-hydroxyethyl]benzene-1,2-diol,



E. 2-[benzyl(methyl)amino]-1-(3,4-dihydroxyphenyl)ethan-1-one,



F. (1*R*)-1-(3,4-dihydroxyphenyl)-2-(methylamino)ethane-1-sulfonic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

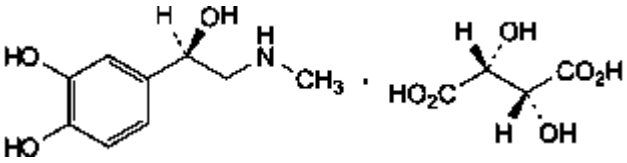
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adrenaline Acid Tartrate / Epinephrine Acid Tartrate

General Notices

(Adrenaline Tartrate, Ph. Eur. monograph 0254)



$C_{13}H_{19}NO_9$ 333.3 *51-42-3*

Action and use

Adrenoceptor agonist.

Preparations

Adrenaline Injection/Epinephrine Injection

Dilute Adrenaline Injection (1 in 10,000)/Dilute Epinephrine Injection (1 in 10,000)

Adrenaline Solution/Epinephrine Solution

Adrenaline and Cocaine Intranasal Solution

Bupivacaine and Adrenaline Injection/Bupivacaine and Epinephrine Injection

Lidocaine and Adrenaline Injection/Lidocaine and Epinephrine Injection

Ph Eur

DEFINITION

(1*R*)-1-(3,4-Dihydroxyphenyl)-2-(methylamino)ethanol hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or greyish-white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 5 g in 50 mL of a 5 g/L solution of *sodium metabisulfite R* and make alkaline by addition of *ammonia R*. Keep the mixture at room temperature for at least 15 min and filter. Reserve the filtrate for identification test C. Wash the precipitate with 3 quantities, each of 10 mL, of *methanol R*. Dry at 80 °C. The specific optical rotation (*2.2.7*) of the residue (adrenaline base) is -53.5 to -50, determined using a 20.0 g/L solution in *0.5 M hydrochloric acid*.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs of adrenaline base prepared as described under identification test A.

Comparison Use adrenaline base prepared as described under identification test A from 50 mg of *adrenaline tartrate CRS* dissolved in 5 mL of a 5 g/L solution of *sodium metabisulfite R*. Keep the mixture at room temperature for at least 30 min. Filter through a sintered-glass filter (*2.1.2*).

C. 0.2 mL of the filtrate obtained in identification test A gives reaction (b) of tartrates (*2.3.1*).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent. Examine the solution immediately.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions protected from light.*

Solvent mixture A Dissolve 5.0 g of *potassium dihydrogen phosphate R* and then 2.6 g of *sodium octanesulfonate R* in *water for chromatography R*, and dilute to 1000 mL with the same solvent (it is usually necessary to stir for at least 30 min to achieve complete dissolution). Adjust to pH 2.8 with *phosphoric acid R*.

Solvent mixture B *acetonitrile R1*, solvent mixture A (130:870 *V/V*).

Test solution Dissolve 75 mg of the substance to be examined in 5 mL of *0.1 M hydrochloric acid* and dilute to 50 mL with solvent mixture B.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solvent mixture B. Dilute 1.0 mL of this solution to 10.0 mL with solvent mixture B.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 1.5 mg of *noradrenaline tartrate CRS* (impurity B) and 1.5 mg of *adrenalone hydrochloride R* (impurity C) in solvent mixture B, add 1.0 mL of the test solution and dilute to 100.0 mL with solvent mixture B.

Reference solution (c) Dissolve the contents of a vial of *adrenaline impurity mixture CRS* (impurities D and E) in 0.1 mL of *0.1 M hydrochloric acid* and 0.9 mL of solvent mixture B.

Reference solution (d) Dissolve 7.5 mg of *adrenaline tartrate with impurity A CRS* in 0.5 mL of *0.1 M hydrochloric acid* and dilute to 5.0 mL with solvent mixture B.

Blank solution *0.1 M hydrochloric acid*, solvent mixture B (1:9 *V/V*).

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, solvent mixture A (5:95 *V/V*);

— *mobile phase B*: *acetonitrile R1*, solvent mixture A (45:55 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	92 → 50	8 → 50
15 - 20	50 → 92	50 → 8
20 - 25	92	8

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *adrenaline impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and E; use the chromatogram supplied with *adrenaline tartrate with impurity A CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity A.

Relative retention With reference to adrenaline (retention time = about 4 min): impurity B = about 0.8; impurity C = about 1.3; impurity A = about 3.2; impurity D = about 3.3; impurity E = about 3.7.

System suitability Reference solution (b):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 3.0 between the peaks due to impurity B and adrenaline.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.7; impurity E = 0.6;

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities B, C*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* for 18 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*, heating gently if necessary. Titrate with *0.1 M perchloric acid* until a bluish-green colour is obtained, using 0.1 mL of *crystal violet solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 33.33 mg of $C_{13}H_{19}NO_9$.

STORAGE

In an airtight container, or preferably in a sealed tube under vacuum or under an inert gas, protected from light.

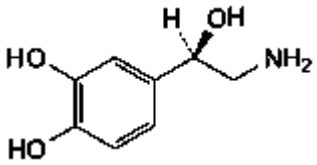
IMPURITIES

Specified impurities *A, B, C, D, E.*

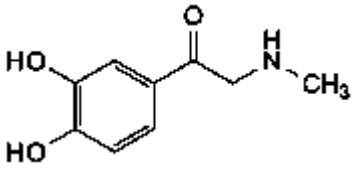
A. unknown structure,

www.webofpharma.com

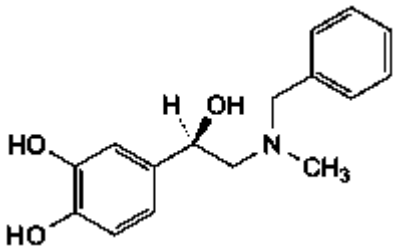
https://thuocngocanh.com/



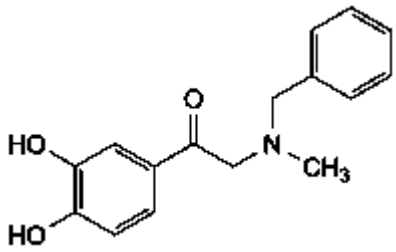
B. (1*R*)-2-amino-1-(3,4-dihydroxyphenyl)ethanol (noradrenaline),



C. 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanone (adrenalone),



D. 4-[(1*R*)-2-(benzylmethylamino)-1-hydroxyethyl]benzene-1,2-diol,



E. 2-(benzylmethylamino)-1-(3,4-dihydroxyphenyl)ethanone.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngoca.net/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adrenaline and Cocaine Intranasal Solution / Epinephrine and Cocaine Intranasal Solution

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Adrenoceptor agonist + local anaesthetic.

DEFINITION

Adrenaline and Cocaine Intranasal Solution contains Adrenaline Acid Tartrate and Cocaine Hydrochloride in a suitable vehicle.

The intranasal solution complies with the requirements stated under Nasal Preparations and with the following requirements. Where appropriate, the intranasal solution also complies with the requirements stated under Unlicensed Medicines.

Content of adrenaline, $C_9H_{13}NO_3$

95.0 to 105.0% of the stated amount.

Content of cocaine hydrochloride, $C_{17}H_{21}NO_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay for adrenaline, the principal peak in the chromatogram obtained with solution (1) has the same retention time as that in the chromatogram obtained with solution (2).

B. In the Assay for cocaine hydrochloride, the principal peak in the chromatogram obtained with solution (1) has the same retention time as that in the chromatogram obtained with solution (2).

C. To 10 ml of the intranasal solution add 2 mL of a 10% w/v solution of *disodium hydrogen orthophosphate* and sufficient *iodinated potassium iodide solution* to produce a brown colour and remove excess iodine by adding 0.1M *sodium thiosulfate* drop wise. A red colour is produced.

D. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 2.0 to 4.0, Appendix V L.

Related substances (for cocaine hydrochloride)

www.webofpharma.com

https://thuocngoaikhoa.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the intranasal solution with sufficient mobile phase to produce a solution containing 0.04% w/v of Cocaine Hydrochloride.
(2) 0.0008% w/v of *benzoylecgonine hydrate* in the mobile phase.
(3) 0.0008% w/v of *benzoic acid* in the mobile phase.
(4) 0.0008% w/v of each of *benzoylecgonine hydrate* and *benzoic acid* in solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Partisil 10 ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of 9M *perchloric acid*, 35 volumes of *methanol* and 64 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to benzoylecgonine and benzoic acid is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to benzoylecgonine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any peak corresponding to benzoic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (2%).

The total impurity content is not greater than 2%.

ASSAY

For adrenaline

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the intranasal solution with sufficient mobile phase to produce a solution containing the equivalent of 0.011% w/v of adrenaline.
(2) 0.02% w/v of *adrenaline acid tartrate BPCRS* in the mobile phase.
(3) 0.02% w/v of *adrenaline acid tartrate BPCRS* and 0.02% w/v of *noradrenaline acid tartrate* in the mobile phase.

www.webofpharma.com

https://thuocngoaikhoa.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 205 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* in a mixture of 950 mL of *water* and 50 mL of *methanol* and adjust the pH to 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{13}NO_3$ in the intranasal solution from the chromatograms obtained and using the declared content of $C_9H_{13}NO_3$ in *adrenaline acid tartrate BPCRS*.

For cocaine hydrochloride

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the intranasal solution containing 40 mg of Cocaine Hydrochloride with sufficient *water* to produce 100 mL.
(2) 0.04% w/v of *cocaine hydrochloride BPCRS* in *water*.
(3) 0.0008% w/v of each of *benzoylecgonine hydrate* and *benzoic acid* in solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Partisil 10 ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of 9M *perchloric acid*, 35 volumes of *methanol* and 64 volumes of *water*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngoaikhoa.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to benzoylecgonine and benzoic acid is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{21}NO_4$,HCl in the intranasal solution from the chromatograms obtained and using the declared content of $C_{17}H_{21}NO_4$,HCl in *cocaine hydrochloride BPCRS*.

STORAGE

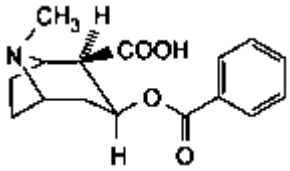
Adrenaline and Cocaine Intranasal Solution should be protected from light.

LABELLING

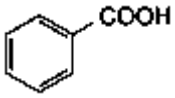
The quantity of adrenaline acid tartrate is stated in terms of the equivalent amount of adrenaline (epinephrine).

IMPURITIES

The impurities limited by the requirements of this monograph include:



1. Benzoylecgonine,



2. Benzoic acid.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngoaidieu.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adrenaline Eye Drops / Epinephrine Eye Drops

General Notices

Neutral Adrenaline Eye Drops

Neutral Epinephrine Eye Drops

Action and use

Adrenoceptor agonist; treatment of glaucoma.

DEFINITION

Adrenaline Eye Drops are a sterile solution of Adrenaline in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of adrenaline, $C_9H_{13}NO_3$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

B. Dilute the eye drops to contain 0.1% w/v of Adrenaline and adjust the pH, if necessary, to neutral or slightly acidic. To 1 mL of this solution add, drop wise, a 0.25% w/v solution of *iron (III) chloride hexahydrate* until a green colour is produced. On the gradual addition of *sodium hydrogen carbonate solution*, the solution changes first to blue and then to red.

C. Dilute the eye drops to contain 0.1% w/v of Adrenaline. To 1 mL of this solution add 2 mL of a 10% w/v solution of *disodium hydrogen orthophosphate* and sufficient *iodinated potassium iodide solution* to produce a brown colour. Remove excess iodine by adding 0.2M *sodium thiosulfate* drop wise; a red colour is produced.

TESTS

Acidity or alkalinity

pH, 5.5 to 7.6, Appendix V L.

Noradrenaline

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute the eye drops to produce a solution containing 0.10% w/v of Adrenaline.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.0018% w/v of *noradrenaline acid tartrate*.

(3) 0.0018% w/v of *noradrenaline acid tartrate* and 0.0018% w/v of *adrenaline acid tartrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution containing 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* in a mixture of 950 mL of *water* and 50 mL of *methanol*, the pH of the mixture being adjusted to 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to noradrenaline is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute the eye drops with sufficient mobile phase to produce a solution containing 0.1% w/v of Adrenaline.

(2) 0.2% w/v of *adrenaline acid tartrate BPCRS* in the mobile phase.

(3) 0.2% w/v of *adrenaline acid tartrate BPCRS* and 0.2% w/v of *noradrenaline acid tartrate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

A solution prepared by adding 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* to a mixture of 950 mL of *water* and 50 mL of *methanol*, the pH of the mixture being adjusted to 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{13}NO_3$ in the eye drops using the declared content of $C_9H_{13}NO_3$ in *adrenaline acid tartrate BPCRS*.

STORAGE

Adrenaline Eye Drops should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adrenaline Injection/Epinephrine Injection

General Notices

Action and use

Adrenoceptor agonist.

DEFINITION

Adrenaline Injection is a sterile, isotonic solution containing either 0.18% w/v of Adrenaline Acid Tartrate or 0.1% w/v of Adrenaline in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of adrenaline, $C_9H_{13}NO_3$

0.0900 to 0.1150% w/v, of which at least 0.0850% w/v is L-adrenaline.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as that in the chromatogram obtained with solution (2).

B. To 10 mL of the injection add 2 mL of a 10% w/v solution of *disodium hydrogen orthophosphate* and sufficient *iodinated potassium iodide solution* to produce a brown colour and remove excess iodine by adding 0.1M *sodium thiosulfate* drop wise. A red colour is produced.

TESTS

Acidity

pH, 2.8 to 4.0, Appendix V L.

Related substances

The total of all impurities from methods A and B is not more than 19.0%.

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. Prepare the solutions immediately before use and protect from light. Store and inject the solutions at 4°, using a cooled autosampler.

(1) Dilute the injection to produce a solution containing the equivalent of 0.005% w/v of Adrenaline.

(2) Dilute 3 volumes of solution (1) to 20 volumes.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.005% w/v of *(±)-adrenaline hydrochloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *β-cyclodextrin hydroxypropyl ether derivative for chiral chromatography* (3 µm) (ORpak CDBS-453 Chiral is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use a column temperature of 10°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of a solution containing 0.2M *potassium chloride* and 0.4% v/v of *glacial acetic acid*, 3 volumes of *acetonitrile* and 96 volumes of 0.2M *potassium chloride*.

When the chromatograms are recorded under the prescribed conditions, the retention time of D-adrenaline (impurity 1) relative to L-adrenaline (retention time about 13 minutes) is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to D-adrenaline (impurity 1) is not greater than the sum of the areas of the peaks due to L-adrenaline and D-adrenaline in the chromatogram obtained with solution (2) (15%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared protected from light.

(1) The preparation being examined.

(2) Dilute 1 volume of solution (1) to 10 volumes with the mobile phase.

(3) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

(4) 0.1% w/v of *adrenaline impurity standard BPCRS* in the mobile phase.

(5) Dilute 1 volume of solution (3) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse Plus C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of adrenaline.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

5 volumes of *methanol* and 95 volumes of a solution containing 0.2mM *disodium edetate*, 5.4mM *sodium heptanesulfonate monohydrate* and 23mM *tetramethylammonium hydrogen sulfate*, adjusted to pH 3.5 with 1M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions the retentions relative to adrenaline (retention time about 18 minutes) are: impurity F, about 0.1; impurity 2, about 0.2; impurity B, about 0.6 and impurity C, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity F and impurity 2 is at least 10.0.

LIMITS

Identify any peaks corresponding to impurities F, 2 and C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of these peaks by the following correction factors: impurity F, 1.3; impurity 2, 0.7 and impurity C, 0.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than 1.8 times the area of the principal peak in the chromatogram obtained with solution (2) (18%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the sum of the areas of any *secondary peaks*, excluding any peak corresponding to impurity F, is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase, prepared protected from light.

(1) Dilute 1 volume of the injection to 10 volumes.
(2) 0.02% w/v of *adrenaline acid tartrate BPCRS*.
(3) 0.02% w/v of *adrenaline acid tartrate BPCRS* and 0.02% w/v of *noradrenaline acid tartrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *methanol R1* and 95 volumes of a solution containing 0.2mM *disodium edetate*, 5.4mM *sodium heptanesulfonate monohydrate* and 23mM *tetramethylammonium hydrogen sulfate*, adjusted to pH 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{13}NO_3$ using the declared content of $C_9H_{13}NO_3$ in *adrenaline acid tartrate BPCRS*.

Calculate the L-adrenaline content using the following equation:

$$C_{LA} = C_A \times \left(\frac{PA_{LA}}{PA_A}\right)$$

where:

C_{LA} = content of L-adrenaline in % w/v

C_A = content of $C_9H_{13}NO_3$ in % w/v, determined in the Assay

PA_{LA} = the area of the peak corresponding to L-adrenaline in the chromatogram obtained with solution (1) of Related substances test A

PA_A = the sum of the areas of the peaks corresponding to L-adrenaline and D-adrenaline in the chromatogram obtained with solution (1) of Related substances test A

STORAGE

Adrenaline Injection should be protected from light and stored at a temperature not exceeding 25°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of adrenaline (epinephrine).

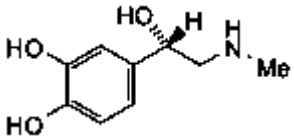
Adrenaline Injection contains the equivalent of adrenaline (epinephrine), 1 in 1000 (1 mg in 1 mL).

IMPURITIES

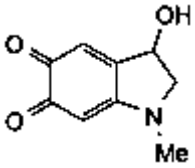
The impurities limited by the requirements of this monograph include impurities B and C listed under Adrenaline Acid Tartrate/Epinephrine Acid Tartrate, impurity F listed under Adrenaline/Epinephrine and:

www.webofpharma.com

https://thuocngocanh.com/



1. (1*S*)-1-(3,4-dihydroxyphenyl)-2-(methylamino)ethan-1-ol (D-adrenaline)



2. 3-hydroxy-2,3-dihydro1*H*-indole-5,6-dione (adrenochrome)

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Adrenaline Solution / Epinephrine Solution

General Notices

Adrenaline Tartrate Solution

Epinephrine Tartrate Solution

Action and use

Adrenoceptor agonist.

DEFINITION

Adrenaline Solution is an isotonic *cutaneous solution* containing 0.18% w/v of Adrenaline Acid Tartrate with a suitable combination of an antioxidant and an antimicrobial preservative in Purified Water.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements. Where appropriate, the solution also complies with the requirements stated under Unlicensed Medicine.

Content of adrenaline, $C_9H_{13}NO_3$

0.09 to 0.11% w/v.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

B. To 1 mL add a 0.25% w/v solution of *iron (III) chloride hexahydrate* drop wise until a green colour is produced. On the gradual addition of *sodium hydrogen carbonate solution*, the solution changes first to blue and then to red.

C. To 10 mL add 2 mL of a 10% w/v solution of *disodium hydrogen orthophosphate* and sufficient *iodinated potassium iodide solution* to produce a brown colour. Remove excess iodine by adding 0.1M *sodium thiosulfate* drop wise; a red colour is produced.

TESTS

Acidity

pH, 2.7 to 3.6, Appendix V L.

Noradrenaline

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) The preparation being examined.

(2) 0.0018% w/v of *noradrenaline acid tartrate*.

(3) 0.0018% w/v of *noradrenaline acid tartrate* and 0.0018% w/v of *adrenaline acid tartrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution containing 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* in a mixture of 950 mL of *water* and 50 mL of *methanol*, the pH of the mixture being adjusted to 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to noradrenaline is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute 1 volume of the preparation being examined to 10 volumes.

(2) 0.02% w/v of *adrenaline acid tartrate BPCRS*.

(3) 0.02% w/v of *adrenaline acid tartrate BPCRS* and 0.02% w/v of *noradrenaline acid tartrate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

Add 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* to a mixture of 50 mL of *methanol* and 950 mL of *water* and adjust the pH of the mixture to 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{13}NO_3$ in the preparation being examined using the declared content of $C_9H_{13}NO_3$ in *adrenaline acid tartrate BPCRS*.

STORAGE

Adrenaline Solution should be kept in a well-filled glass container suitable for parenteral preparations, Appendix XIX B, and should be protected from light.

LABELLING

The label states (1) the date after which the solution is not intended to be used; (2) the conditions under which it should be stored.

The quantity of active ingredient is stated in terms of the equivalent amount of adrenaline (epinephrine).

The label indicates the pharmaceutical form as ‘cutaneous solution’.

Adrenaline Solution contains the equivalent of adrenaline (epinephrine), 1 in 1000 (1 mg in 1 mL).

When a solution of adrenaline hydrochloride is prescribed or demanded, a solution complying with the requirements of this monograph may be dispensed or supplied.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Agar

General Notices

(Ph. Eur. monograph 0310)

Action and use

Excipient.

Ph Eur

DEFINITION

Polysaccharides from various species of Rhodophyceae mainly belonging to the genus *Gelidium*. It is prepared by treating the algae with boiling water; the extract is filtered whilst hot, concentrated and dried.

CHARACTERS

Appearance

Powder or crumpled strips 2-5 mm wide or sometimes flakes, colourless or pale yellow, translucent, somewhat tough and difficult to break, becoming more brittle on drying.

Mucilaginous taste.

IDENTIFICATION

A. Examine under a microscope. When mounted in 0.005 M iodine, the strips or flakes are partly stained brownish-violet. Magnified 100 times, they show the following diagnostic characters: numerous minute, colourless, ovoid or rounded grains on an amorphous background; occasional brown, round or ovoid spores with a reticulated surface, measuring up to 60 µm, may be present. Reduce to a powder, if necessary. The powder is yellowish-white. Examine under a microscope using 0.005 M iodine. The powder presents angular fragments with numerous grains similar to those seen in the strips and flakes; some of the fragments are stained brownish-violet.

B. Dissolve 0.1 g with heating in 50 mL of *water R*. Cool. To 1 mL of the mucilage carefully add 3 mL of *water R* so as to form 2 separate layers. Add 0.1 mL of *0.05 M iodine*. A dark brownish-violet colour appears at the interface. Mix. The liquid becomes pale yellow.

C. Heat 5 mL of the mucilage prepared for identification test B on a water-bath with 0.5 mL of *hydrochloric acid R* for 30 min. Add 1 mL of *barium chloride solution R1*. A white turbidity develops within 30 min.

D. Heat 0.5 g with 50 mL of *water R* on a water-bath until dissolved. Only a few fragments remain insoluble. During cooling, the solution gels between 35 °C and 30 °C. Heat the gel thus obtained on a water-bath; it does not liquefy below 80 °C.

TESTS

Swelling index (*2.8.4*)

www.webofpharma.com

https://thuocngocanh.com/

Minimum 10 and within 10 per cent of the value stated on the label, determined on the powdered herbal drug (355) (2.9.12).

Insoluble matter

Maximum 1.0 per cent.

To 5.00 g of the powdered herbal drug (355) (2.9.12) add 100 mL of *water R* and 14 mL of *dilute hydrochloric acid R*. Boil gently for 15 min with frequent stirring. Filter the hot liquid through a tared, sintered-glass filter (160) (2.1.2), rinse the filter with hot *water R* and dry at 100-105 °C. The residue weighs a maximum of 50 mg.

Gelatin

To 1.00 g add 100 mL of *water R* and heat on a water-bath until dissolved. Allow to cool to 50 °C. To 5 mL of this solution add 5 mL of *picric acid solution R*. No turbidity appears within 10 min.

Loss on drying (2.2.32)

Maximum 20.0 per cent, determined on 1.000 g of the powdered herbal drug (355) (2.9.12) by drying in an oven at 105 °C.

Total ash (2.4.16)

Maximum 5.0 per cent.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

LABELLING

The label states the swelling index.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

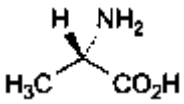
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alanine

General Notices

(Ph. Eur. monograph 0752)



$C_3H_7NO_2$ 89.1 *56-41-7*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Aminopropanoic acid.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *alanine CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 50 mL with the same solvent.

Reference solution Dissolve 10 mg of *alanine CRS* in *water R* and dilute to 50 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 0.5 g in a mixture of 0.25 mL of *hydrochloric acid R1*, 0.5 mL of a 100 g/L solution of *sodium nitrite R* and 1 mL of *water R*. Shake; gas is given off. Add 2 mL of *dilute sodium hydroxide solution R*, followed by 0.25 mL of *iodinated potassium iodide solution R*. After about 30 min, a yellow precipitate is formed.

TESTS

Solution S

Dissolve 2.5 g in *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dilute 10 mL of solution S to 20 mL with *water R*.

Specific optical rotation (*2.2.7*)

+ 13.5 to + 15.5 (dried substance).

Dissolve 2.50 g in *hydrochloric acid R1* and dilute to 25.0 mL with the same acid.

Ninhydrin-positive substances

Amino acid analysis (*2.2.56*). For analysis, use Method 1.

www.webofpharma.com

https://thuvienthuocngocanh.com/

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A dilute hydrochloric acid R1 or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of proline R in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of ammonium standard solution (100 ppm NH_4) R to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of isoleucine R and 30 mg of leucine R in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— resolution: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of alanine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 200 ppm.

www.webofpharma.com

https://thuocngocanh.com/

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 80.0 mg in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 8.91 mg of $C_3H_7NO_2$.

STORAGE

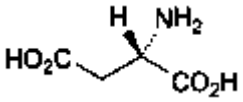
Protected from light.

IMPURITIES

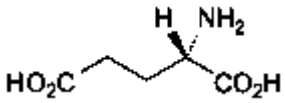
www.webofpharma.com

https://thuvienthuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B.*



A. (2*S*)-2-aminobutanedioic acid (aspartic acid),



B. (2*S*)-2-aminopentanedioic acid (glutamic acid).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

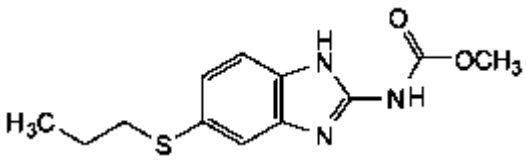
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Albendazole

General Notices

(Ph. Eur. monograph 1386)



$C_{12}H_{15}N_3O_2S$ 265.3 *54965-21-8*

Action and use

Benzimidazole antihelminthic.

Preparations

Albendazole Oral Suspension

Albendazole Oral Suspension with Minerals

Ph Eur

DEFINITION

Methyl *N*-[5-(propylsulfanyl)-1*H*-benzimidazol-2-yl]carbamate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish powder.

Solubility

Practically insoluble in water, freely soluble in anhydrous formic acid, very slightly soluble in methylene chloride, practically insoluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison albendazole CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methylene chloride R, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Dissolve 0.10 g in a mixture of 10 volumes of *anhydrous formic acid R* and 90 volumes of methylene chloride R and dilute to 10 mL with the same mixture of solvents.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture sulfuric acid R, methanol R (1:99 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in 5 mL of the solvent mixture and immediately dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of albendazole for system suitability CRS (containing impurities B, C, E, F and H) in 1 mL of the solvent mixture and dilute to 10 mL with the mobile phase.

Reference solution (c) Dilute 1 mL of the solvent mixture to 10 mL with the mobile phase. Use 1 mL of this solution to dissolve the contents of a vial of albendazole impurity mixture CRS (containing impurities A and D).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase 1.67 g/L solution of ammonium dihydrogen phosphate R, methanol R (30:70 *V/V*).

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL.

Run time Twice the retention time of albendazole.

Identification of impurities Use the chromatogram supplied with *albendazole impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and D; use the chromatogram supplied with *albendazole for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B + C, E, F and H.

Relative retention With reference to albendazole (retention time = about 11 min): impurity D = about 0.35; impurities B and C = about 0.40; impurity E = about 0.45; impurity A = about 0.48; impurity F = about 0.57; impurity H = about 0.66.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B + C and E.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.7; impurities B and C = 1.4; impurity D = 1.9; impurity E = 1.4;

— for each impurity, use the concentration of albendazole in reference solution (a).

Limits:

— *impurity H*: maximum 0.6 per cent;

— *impurity F*: maximum 0.5 per cent;

— *impurity A*: maximum 0.4 per cent;

— *sum of impurities B and C*: maximum 0.4 per cent;

— *impurity E*: maximum 0.3 per cent;

— *impurity D*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

In order to avoid overheating during the titration, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.250 g in 3 mL of *anhydrous formic acid R* and add 40 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 26.53 mg of $C_{12}H_{15}N_3O_2S$.

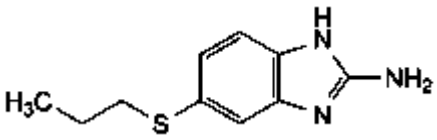
STORAGE

Protected from light.

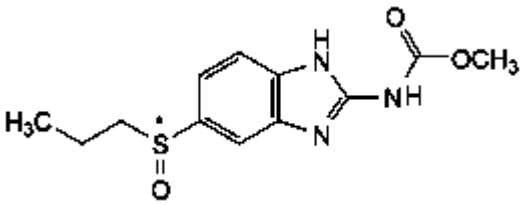
IMPURITIES

Specified impurities *A, B, C, D, E, F, H.*

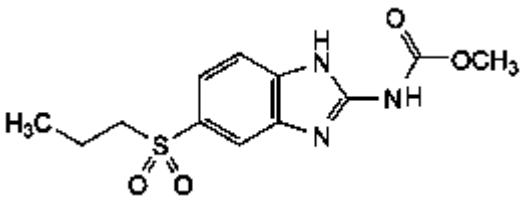
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G, I, J, K, L.*



A. 5-(propylsulfanyl)-1*H*-benzimidazol-2-amine,



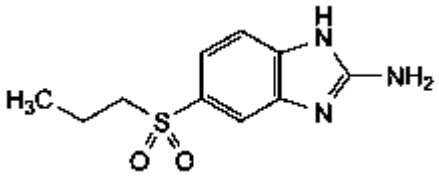
B. methyl *N*-[5-(propylsulfinyl)-1*H*-benzimidazol-2-yl]carbamate,



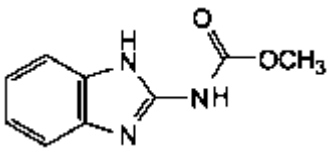
C. methyl *N*-[5-(propylsulfonyl)-1*H*-benzimidazol-2-yl]carbamate,

www.webofpharma.com

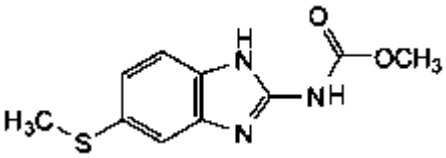
https://thuocngocanh.com/



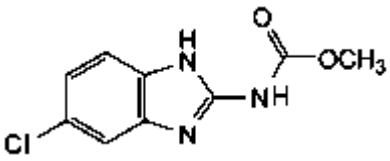
D. (2-amino-1*H*-benzimidazol-5-yl)propyl-λ^6-sulfanedione,



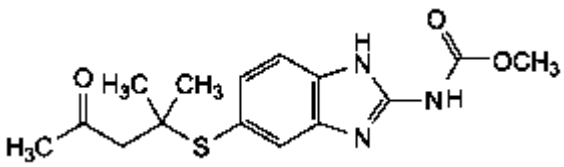
E. methyl *N*-(1*H*-benzimidazol-2-yl)carbamate,



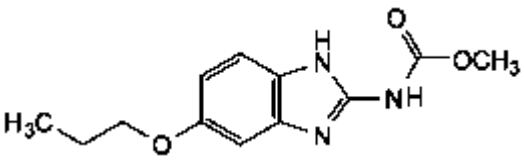
F. methyl *N*-[5-(methylsulfanyl)-1*H*-benzimidazol-2-yl]carbamate,



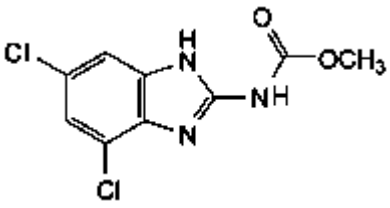
G. methyl *N*-(5-chloro-1*H*-benzimidazol-2-yl)carbamate,



H. methyl *N*-[5-[(2-methyl-4-oxopentan-2-yl)sulfanyl]-1*H*-benzimidazol-2-yl]carbamate,



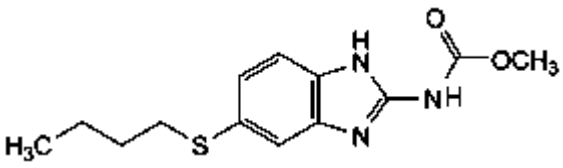
I. methyl *N*-(5-propoxy-1*H*-benzimidazol-2-yl)carbamate,



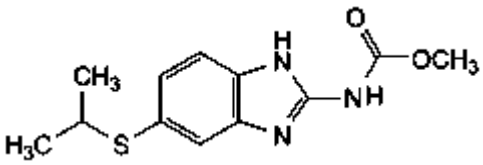
www.webofpharma.com

https://thuocngocanh.com/

J. methyl *N*-(4,6-dichloro-1*H*-benzimidazol-2-yl)carbamate,



K. methyl *N*-[5-(butylsulfanyl)-1*H*-benzimidazol-2-yl]carbamate,



L. methyl *N*-[5-[(propan-2-yl)sulfanyl]-1*H*-benzimidazol-2-yl]carbamate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alcoholic Iodine Solution

General Notices

Alcoholic Iodine Cutaneous Solution

DEFINITION

Alcoholic Iodine Solution is a *cutaneous solution*.

Iodine	25 g
Potassium Iodide	25 g
Purified Water	25 mL
Ethanol (90 per cent)	Sufficient to produce 1000 mL

Extemporaneous preparation

The following directions apply.

Dissolve the Potassium Iodide and the Iodine in the Purified Water and add sufficient Ethanol (90 per cent) to produce 1000 mL.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of iodine, I

2.4 to 2.7% w/v.

Content of potassium iodide, KI

2.4 to 2.7% w/v.

Ethanol content

83 to 88% v/v, Appendix VIII F.

ASSAY

For iodine

Dilute 10 mL with 20 mL of *water* and titrate with 0.1M *sodium thiosulfate VS*. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 12.69 mg of I.

For potassium iodide

www.webofpharma.com

https://thuocngocanh.com/

To 10 mL add 30 mL of *water* and 50 mL of *hydrochloric acid* and titrate with *0.05M potassium iodate VS* until the dark brown solution which is produced becomes pale brown. Add 1 mL of *amaranth solution* and continue the titration until the red colour just changes to pale yellow. From the number of mL of *0.05M potassium iodate VS* required subtract half the number of mL of 0.1M *sodium thiosulfate VS* required in the Assay for iodine. Each mL of the remainder is equivalent to 16.60 mg of KI.

STORAGE

Alcoholic Iodine Solution should be kept in a well-closed container, the materials of which are resistant to iodine.

When iodine tincture is prescribed or demanded Alcoholic Iodine Solution shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

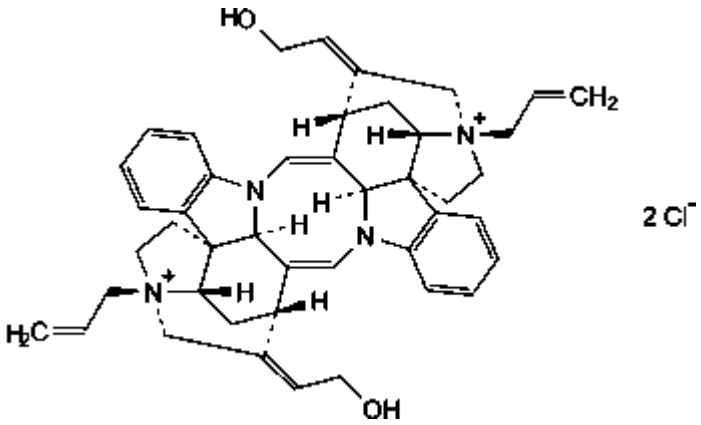
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alcuronium Chloride

General Notices

(Ph. Eur. monograph 1285)



$C_{44}H_{50}Cl_2N_4O_2$ 738 *15180-03-7*

Action and use

Non-depolarizing neuromuscular blocker.

Ph Eur

DEFINITION

(1*R*,3a*S*,10*S*,11a*S*,12*R*,14a*S*,19a*S*,20b*S*,21*S*,22a*S*,23*E*,26*E*)-23,26-bis(2-Hydroxyethylidene)-1,12-bis(prop-2-enyl)-2,3,11,11a,13,14,22,22a-octahydro-10*H*,21*H*-1,21:10,12-diethano-19a*H*,20b*H*-[1,5]diazocino[1,2,3-*lm*:5,6,7-*l′m′*]dipyrrolo[2′,3′-*d*:2″,3′′:*d′*]dicarbazolediium dichloride (4,4′-didesmethyl-4,4′-bis(prop-2-enyl)toxiferin I dichloride).

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly greyish-white, crystalline powder.

Solubility

Freely soluble in water and in methanol, soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

www.webofpharma.com

https://thatluocngocanh.com/

Carry out the identification, tests and assay as rapidly as possible avoiding exposure to actinic light.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *alcuronium chloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *alcuronium chloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase Mix 15 volumes of a 58.4 g/L solution of *sodium chloride R*, 35 volumes of *dilute ammonia R2* and 50 volumes of *methanol R*.

Application 10 µL.

Development Over a path of 15 cm.

Drying In air for 10 min.

Detection Spray with *0.1 M ammonium and cerium nitrate*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.250 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6, BY_6 or B_6 (2.2.2, *Method I*).

Acidity or alkalinity

www.webofpharma.com

https://thuocngocanh.com/

To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M hydrochloric acid*. The solution is red. Add 0.4 mL of *0.01 M sodium hydroxide*. The solution is yellow.

Specific optical rotation (*2.2.7*)

-430 to -451 (anhydrous substance), determined on solution S.

Propan-2-ol (*2.4.24, System A*)

Maximum 1.0 per cent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mix 100 mL of *methanol R*, 200 mL of *acetonitrile R* and 200 mL of a 6.82 g/L solution of *potassium dihydrogen phosphate R*. Dissolve 1.09 g of *sodium laurylsulfonate for chromatography R* in the mixture and adjust the apparent pH to 8.0 with a 100 g/L solution of *sodium hydroxide R*.

Test solution Dissolve 0.20 g of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 0.5 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 4.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (d) To 5.0 mL of the test solution add 5.0 mg of *allylstrychnine bromide CRS*, dissolve in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 200 mL of *methanol R*, 400 mL of *acetonitrile R* and 400 mL of a 6.82 g/L solution of *potassium dihydrogen phosphate R*. Dissolve 2.18 g of *sodium laurylsulfonate for chromatography R* in the mixture and adjust the apparent pH to 5.4 with a 100 g/L solution of *phosphoric acid R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time Twice the retention time of alcuronium.

System suitability Reference solution (d):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 4.0 between the peaks due to *N*-allylstrychnine and alcuronium.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and not more than one of the peaks has an area greater than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (2.5.12)

Maximum 5.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g by stirring in 70 mL of *acetic anhydride R* for 1 min. Titrate with *0.1 M perchloric acid* until the colour changes from violet-blue to greenish-blue, using 0.1 mL of *crystal violet solution R* as indicator.

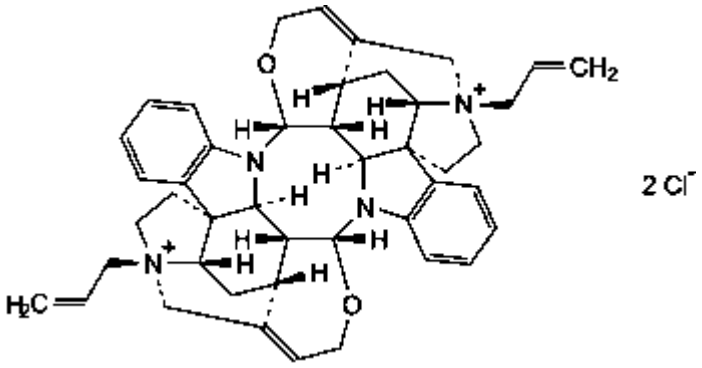
1 mL of *0.1 M perchloric acid* is equivalent to 36.9 mg of $C_{44}H_{50}Cl_2N_4O_2$.

STORAGE

In an airtight container under nitrogen, protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities A, B.

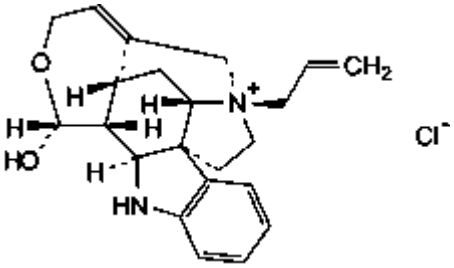


A. (1*R*,3a*S*,9*R*,9a*R*,10*R*,11a*S*,12*R*,14a*S*,19a*S*,20*R*,20a*R*,20b*S*,21*R*,22a*S*)-1,12-bis(prop-2-enyl)-2,3,9a,11,11a,13,14,19a,20a,21,22,22a-dodecahydro-10*H*,20b*H*-1,23:12,27-dimethano-9,10:20,21-bis(epoxyprop[2]eno)-9*H*,20*H*-[1,5]diazocino[1,2,3-*lm*:5,6,7-*l'm'*]dipyrrolo[2',3'-

www.webofpharma.com

https://thuocngocanh.com/

d:2″,3″:*d*′]dicarbazolediium dichloride (4,4′-diallylcaracurin V dichloride),



B. (4b*S*,7*R*,7a*S*,8a*R*,13*R*,13a*R*,13b*S*)-13-hydroxy-7-(prop-2-enyl)-5,6,7a,8,8a,11,13,13a,13b,14-decahydro-7,9-methano-7*H*-oxepino[3,4-*a*]pyrrolo[2,3-*d*]carbazolium chloride ((4*R*,17*R*)-4-allyl-17,18-epoxy-17-hydroxy-19,20-didehydrocuranium chloride).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alendronic Acid and Colecalciferol Tablets

General Notices

Sodium Alendronate and Colecalciferol Tablets

Action and use

Bisphosphonate + Vitamin D3 analogue.

DEFINITION

Alendronic Acid and Colecalciferol Tablets contain Sodium Alendronate Trihydrate and Colecalciferol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of alendronic acid, $C_4H_{13}NO_7P_2$

92.5 to 105.0% of the stated amount.

Content of colecalciferol, $C_{27}H_{44}O$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing the equivalent of 70 mg of alendronic acid with 50 mL of *water* for 30 minutes and filter.

(2) 0.2% w/v of *sodium alendronate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *cellulose*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of warm air, spray with *ninhydrin solution*, heat at 105° and examine in daylight.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 8 volumes of 2.5% v/v *trichloroacetic acid* and 11 volumes of *methanol*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) is similar in size, position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay for alendronic acid, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions. *Prepare the solutions immediately before use*.

Solution A A solution containing 1% w/v of *squalane* and 0.01% w/v of *butylated hydroxytoluene* in *ethylene chloride*.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 1 mg of Colecalciferol with 20 mL of *methanol*, centrifuge and filter. Evaporate the filtrate to dryness and dissolve the residue immediately in 0.4 mL of solution A.

(2) 0.25% w/v of *colecalciferol BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in current of warm air, and spray with *sulfuric acid*.

MOBILE PHASE

0.01% w/v of *butylated hydroxytoluene* in a mixture of equal volumes of *cyclohexane* and *peroxide-free ether*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in size, position and colour to that in the chromatogram obtained with solution (2).

D. In the Assay for colecalciferol, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

For alendronic acid

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) After 15 minutes withdraw a sample of the medium and filter (Whatman GF/C is suitable). Use the filtered dissolution medium diluted, if necessary, to produce a solution expected to contain the equivalent of 0.0078% w/v of alendronic acid.

(2) 0.01% w/v of *sodium alendronate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *anion exchange resin* (Waters IC PAK Anion HC is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a conductivity detector, maintained at 35°.

(f) Inject 100 µL of each solution.

MOBILE PHASE

0.59% w/v of *succinic acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of the peak due to alendronic acid is about 7 minutes.

DETERMINATION OF CONTENT

Calculate the total content of alendronic acid, $C_4H_{13}NO_7P_2$ in the medium using the declared content of $C_4H_{12}NNaO_7P_2$ in *sodium alendronate BPCRS* and the peak heights in the chromatograms obtained. Each mg of $C_4H_{12}NNaO_7P_2$ is equivalent to 0.9189 mg of $C_4H_{13}NO_7P_2$.

LIMITS

The amount of alendronic acid released is not less than 75% (Q) of the stated amount.

For colecalciferol

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 500 mL of a mixture of 3% w/v of *sodium lauryl sulfate* and 0.9% w/v of *sodium chloride*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 15 minutes withdraw a sample of the medium and filter (Whatman GF/C is suitable). Use the filtered dissolution medium diluted with medium, if necessary, to produce a solution expected to contain 0.000014% w/v of colecalciferol.

(2) Dilute 1 volume of a solution containing 0.0014% w/v of *colecalciferol BPCRS* in *methanol* to 100 volumes with the dissolution medium.

(3) Heat an aliquot of solution (2) on a water bath at 50° for 2 hours (generation of pre-colecalciferol).

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Phenomenex Synergi-Hydro RP is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 269 nm.

(f) Inject 150 µL of each solution.

MOBILE PHASE

methanol (96%).

When the chromatograms are recorded under the prescribed conditions the retention times of pre-colecalciferol and colecalciferol are about 11 minutes and 12 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to colecalciferol and pre-colecalciferol is at least 1.2.

DETERMINATION OF CONTENT

Use the sum of the peak areas of colecalciferol and pre-colecalciferol. Calculate the total content of colecalciferol, $C_{27}H_{44}O$, in the medium using the declared content of $C_{27}H_{44}O$, in *colecalciferol BPCRS*.

LIMITS

The amount of colecalciferol released is not less than 75% (Q) of the stated amount.

Related substances

For alendronic acid

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Derivatise each solution prior to analysis.

Solution A A solution containing 0.294% w/v of *sodium citrate* and 0.142% w/v of *anhydrous disodium hydrogen orthophosphate*, adjusted to pH 8.0 with *orthophosphoric acid*.

(1) Mix a quantity of the powdered tablets containing the equivalent of 30 mg of alendronic acid with a 2.94% w/v solution of *sodium citrate*, dilute to 50 mL with the same solvent and filter.

(2) 0.00012% w/v of 4-aminobutanoic acid in 2.94% w/v *sodium citrate*.

(3) Dilute 1 volume of solution (1) to 100 volumes with a 2.94% w/v solution of *sodium citrate*, further dilute 1 volume of this solution to 5 volumes with the same solvent.

(4) 0.06% w/v of *sodium alendronate BPCRS* and 0.01% w/v of *4-aminobutanoic acid*(impurity A) in 2.94% w/v *sodium citrate*.

(5) 0.000065% w/v of *sodium alendronate BPCRS* in 2.94% w/v of *sodium citrate*.

Derivatisation procedure Transfer 5 mL of solutions (1) to (5) separately into screw-cap centrifuge tubes, add 5 mL of a 1.91% w/v solution of sodium tetrahydroborate, 10 mL of a 0.2% w/v solution of *(9-fluorenyl)methyl chloroformate* in *acetonitrile*, shake for 1 minute

www.webofpharma.com

https://thuocngocanh.com/

and allow to stand at room temperature for 30 minutes, add 20 mL of *dichloromethane* and shake vigorously for 1 minute; centrifuge and use the aqueous layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.1 mm) packed with *styrene-divinylbenzene copolymer* (10 µm) (Hamilton PRP-1 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 266 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 85 volumes of solution A and 15 volumes of *acetonitrile*.

Mobile phase B 30 volumes of solution A and 70 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	100	0	isocratic
15-25	100→50	0→50	linear gradient
25-27	50→0	50→100	linear gradient
27-32	0→100	100→0	linear gradient
32-40	100	0	re-equilibration

The retention time of the peaks due to alendronic acid and 4-aminobutanoic acid, as their derivatives, are about 4 minutes and about 9 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the two principal peaks is at least 10.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminobutanoic acid is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of all impurities is not more than 0.5%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

www.webofpharma.com

https://thuocngocanh.com/

Related substances

For colecalciferol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 0.56 mg of Colecalciferol with 5 mL of *water*. Add 25 mL of *ethanol*, stir for 30 minutes, add sufficient *methanol* to produce 50 mL and centrifuge.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) Heat 10 mL of a 0.00112% w/v solution of *colecalciferol BPCRS* in *methanol* in a capped vessel to 50° for two hours (generation of pre-colecalciferol).

(4) Dilute 1 volume of solution (2) to 10 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Supelco Discovery HS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use an auto-sampler temperature of 5°.

(f) Use a detection wavelength of 266 nm.

(g) Inject 20 µL of each solution.

(h) For solution (1), allow the chromatography to proceed for 2.5 times the retention time of colecalciferol

MOBILE PHASE

methanol (96%).

The retention time of the peaks due to pre-colecalciferol and colecalciferol are about 12 and 13 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 1.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the sum of the areas of the peaks due to pre-colecalciferol and colecalciferol in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the sum of the areas of the peaks due to pre-colecalciferol and colecalciferol in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak due to pre-colecalciferol and any peak with an area less than the sum of the areas of the peaks due to pre-colecalciferol and colecalciferol in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

www.webofpharma.com

https://thuocngocanh.com/

For colecalciferol

For tablets containing less than 2 mg and/or less than 2% w/w of colecalciferol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse one whole tablet in 5 mL of *water*, add 25 mL of *ethanol* and stir for 30 minutes, add sufficient *methanol* to produce 0.00014% w/v of Colecalciferol and filter (Whatman GF/C is suitable).
(2) 0.00014% w/v of *colecalciferol BPCRS* in *methanol*.
(3) Heat 10 mL solution of a 0.00112% w/v of *colecalciferol BPCRS* in *methanol* in a capped vessel to 50° for two hours (generation of pre-colecalciferol).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances (for colecalciferol) may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 1.0.

DETERMINATION OF CONTENT

Combine the peak areas of colecalciferol and pre-colecalciferol. Calculate the total content of colecalciferol, $C_{27}H_{44}O$, in the tablets using the declared content of $C_{27}H_{44}O$, in *colecalciferol BPCRS*.

ASSAY

For alendronic acid

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing the equivalent of 0.1 g of alendronic acid with 200 mL of *water* for 30 minutes with the aid of ultrasound and occasional shaking, add sufficient *water* to produce 250 mL and centrifuge.
(2) 0.052% w/v of *sodium alendronate BPCRS* in *water*.
(3) 0.02% w/v of *sodium alendronate BPCRS* and 0.01% w/v of *sodium dihydrogen orthophosphate* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.1 mm) packed with *styrene-divinylbenzene copolymer for chromatography* (10 µm) (Hamilton PRP-X100 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.6 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 100 µL of each solution.
(g) The method is validated to measure the drop in absorbance due to alendronic acid and an inverted peak will be observed.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

0.007M *nitric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of the inverted peak due to alendronic acid is about 3.5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of alendronic acid, $C_4H_{13}NO_7P_2$ in the tablets using the declared content of $C_4H_{12}NNaO_7P_2$ in *sodium alendronate BPCRS* and the peak depth in the chromatograms obtained. Each mg of $C_4H_{12}NNaO_7P_2$ is equivalent to 0.9189 mg of $C_4H_{13}NO_7P_2$.

For colecalciferol

Use the average of the individual results obtained in the test for Uniformity of content.

LABELLING

The quantity of sodium alendronate is stated in terms of the equivalent amount of alendronic acid.

The quantity of Colecalciferol is expressed in terms of both mg and IU.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Colecalciferol and impurities A and D listed under *Sodium Alendronate Trihydrate*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alendronic Acid Tablets

General Notices

Sodium Alendronate Tablets

Action and use

Bisphosphonate; treatment of osteoporosis.

DEFINITION

Alendronic Acid Tablets contain Sodium Alendronate Trihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of alendronic acid, $C_4H_{13}NO_7P_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix a quantity of the powdered tablets containing the equivalent of 76 mg of alendronic acid with 50 mL of *water* for 30 minutes with the aid of ultrasound and occasional shaking, and filter.

(2) 0.2% w/v of *sodium alendronate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *cellulose*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of warm air, spray with *ninhydrin solution*, heat at 100° to 105° for 15 minutes and examine.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 8 volumes of 2.5% v/v *trichloroacetic acid* and 11 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw a sample of the medium and filter (Whatman GF/C is suitable). Use the filtered sample diluted with the dissolution medium, if necessary, to produce a solution expected to contain the equivalent of 0.00084% w/v of alendronic acid.

(2) 0.0011% w/v of *sodium alendronate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *anion exchange resin* (7 µm) (Allsep Anion is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a refractive index detector, maintained at 40°.

(f) Inject 100 µL of each solution.

MOBILE PHASE

0.02% v/v of *formic acid*, pH adjusted to 3.5 with *2M sodium hydroxide*.

DETERMINATION OF CONTENT

Calculate the total content of $C_4H_{13}NO_7P_2$ in the medium using the declared content of $C_4H_{12}NNaO_7P_2$ in *sodium alendronate BPCRS*.

Each mg of $C_4H_{12}NNaO_7P_2$ is equivalent to 0.9189 mg of $C_4H_{13}NO_7P_2$.

LIMITS

The amount of alendronic acid released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Buffer solution Prepare a solution containing 0.294% w/v of *sodium citrate* and 0.142% w/v of *anhydrous disodium hydrogen orthophosphate*, adjusted to pH 8.0 using *orthophosphoric acid* and filter.

Solution A 2.94% w/v of *sodium citrate* in *water*.

www.webofpharma.com

https://thuocngocanh.com/

Solution B 1.91% w/v of *sodium borate* in *water*.

Solution C 0.02% w/v of *(9-fluorenyl)methyl chloroformate* in *acetonitrile*. Prepare immediately before use.

(1) Mix a quantity of the powdered tablets containing the equivalent of 23 mg of alendronic acid with solution A and make up to 50 mL with the same solvent. Mix and filter (Whatman GF/C is suitable), discarding the first 5 mL of filtrate. To 5 mL of the filtrate in a screw cap centrifuge tube add 5 mL of solution B and 10 mL of solution C, shake for 1 minute and allow to stand at room temperature for 30 minutes, add 20 mL of *dichloromethane* and shake vigorously for 1 minute; centrifuge and use the aqueous layer.
(2) To 5 mL of a 0.0003% w/v solution of *4-aminobutanoic acid* in solution A in a screw cap centrifuge tube, add 5 mL of solution B and 10 mL of solution C, shake for 45 seconds and allow to stand at room temperature for 30 minutes, add 20 mL of *dichloromethane* and shake vigorously for 1 minute, centrifuge and use the aqueous layer.
(3) To 5 mL of a solution containing 0.06% w/v of *sodium alendronate BPCRS* and 0.01% w/v of *4-aminobutanoic acid* in solution A in a screw cap centrifuge tube add 5 mL of solution B and 10 mL of solution C, shake for 45 seconds and allow to stand at room temperature for 30 minutes, add 20 mL of *dichloromethane* and shake vigorously for 1 minute; centrifuge and use the aqueous layer.
(4) To 5 mL of a solution containing 0.00012% of *sodium alendronate BPCRS* in solution A in a screw cap centrifuge tube, add 5 mL of solution B and 10 mL of solution C, shake for 45 seconds and allow to stand at room temperature for 30 minutes. Add 20 mL of *dichloromethane* and shake vigorously for 1 minute, centrifuge and use the aqueous layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.1 mm) packed with *styrene-divinylbenzene copolymer* (10 µm) (Hamilton PRP-1 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.8 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 266 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 3 volumes of *acetonitrile* and 17 volumes of buffer solution.

Mobile phase B 3 volumes of buffer solution and 7 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	100	0	isocratic
15-25	100→50	0→50	linear gradient
25-27	50→0	50→100	linear gradient
27-32	0→100	100→0	linear gradient
32-40	100	0	re-equilibration

The retention time of the peaks due to alendronic acid and aminobutanoic acid, as their derivatives, are about 5 minutes and about 9.5 minutes respectively.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 10.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminobutanoic acid is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Impurities B and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 0.1 g of alendronic acid, add 20 mL of *water* and mix with the aid of ultrasound for 30 minutes. Add sufficient *water* to produce 25 mL and filter (Whatman GF/C is suitable).
(2) 0.0024% w/v of *orthophosphoric acid* (impurity B) and 0.002% w/v of *phosphorous acid* (impurity C).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used. Allow the chromatography to proceed for twice the retention time of the principal peak.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to alendronic acid (retention time, about 17 minutes) are: impurity B, about 1.3 and impurity C, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *signal-to-noise* ratios of the peaks due to impurity B and impurity C are at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B or impurity C is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing the equivalent of 50 mg of alendronic acid with 20 mL of *water* for 30 minutes with the aid of ultrasound and occasional shaking, and agitate until cool, add sufficient *water* to produce 25 mL, mix and filter (Whatman GF/C is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.22% w/v of *sodium alendronate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_4H_{13}NO_7P_2$ in the tablets using the declared content of $C_4H_{12}NNaO_7P_2$ in *sodium alendronate BPCRS*. Each mg of $C_4H_{12}NNaO_7P_2$ is equivalent to 0.9189 mg of $C_4H_{13}NO_7P_2$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of alendronic acid.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Sodium Alendronate Trihydrate.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

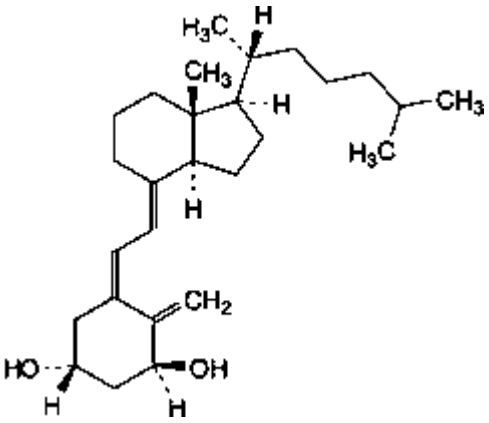
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alfacalcidol

General Notices

(Ph. Eur. monograph 1286)



$C_{27}H_{44}O_2$ 400.6 *41294-56-8*

Action and use

Vitamin D analogue.

Ph Eur

DEFINITION

(1*S*,3*R*,5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1,3-diol.

Content

97.0 per cent to 102.0 per cent.

A reversible isomerisation to pre-alfacalcidol takes place in solution, depending on temperature and time. The activity is due to both compounds (see Assay).

CHARACTERS

Appearance

White or almost white crystals.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in fatty oils.

It is sensitive to air, heat and light.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of alfacalcidol*.

B. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Carry out the test as rapidly as possible, avoiding exposure to light and air, and prepare the solutions immediately before use.*

Test solution Dissolve 5.0 mg of the substance to be examined in 25.0 mL of *acetonitrile R* and dilute to 50.0 mL with *water R*.

Reference solution (a) Dissolve 5.0 mg of *alfacalcidol CRS* in 25.0 mL of *acetonitrile R* and dilute to 50.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*. Dilute 1.0 mL of this solution to 20.0 mL with the same mixture of solvents.

Reference solution (c) Dissolve 2 mg of *alfacalcidol for system suitability A CRS* (containing impurities A and D) in 10 mL of *acetonitrile R* and dilute to 20 mL with *water R*. Allow to stand at room temperature for about 2 h, ensuring that the signal-to-noise ratio of the peak due to pre-alfacalcidol is between 25 and 300.

Reference solution (d) Dissolve 2 mg of *alfacalcidol impurity B CRS* in 10 mL of *acetonitrile R* and dilute to 20 mL with *water R*. Dilute 1.0 mL of the solution to 200.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 32 °C.

Mobile phase *methanol R*, *water for chromatography R*, *acetonitrile R* (15:17:68 *V/V/V*).

Flow rate 0.3 mL/min.

Detection Spectrophotometer at 264 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 5 µL of the test solution and reference solutions (b), (c) and (d).

Run time Twice the retention time of alfacalcidol.

Identification of impurities Use the chromatogram supplied with *alfacalcidol for system suitability A CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and D and pre-alfacalcidol; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity B.

Relative retention With reference to alfacalcidol (retention time = about 15 min): pre-alfacalcidol = about 0.91; impurity A = about 0.94; impurity D = about 0.96; impurity B = about 1.1.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity D and alfacalcidol;

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to pre-alfacalcidol; minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Limits:

— *impurities A, B, D*: for each impurity, maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to pre-alfacalcidol.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{27}H_{44}O_2$ taking into account the assigned content of *alfacalcidol CRS* and, if present, the peak due to pre-alfacalcidol.

STORAGE

Under nitrogen, in an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

The contents of an opened container are to be used immediately.

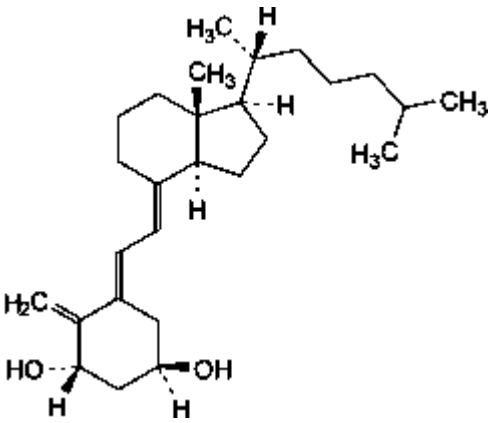
IMPURITIES

www.webofpharma.com

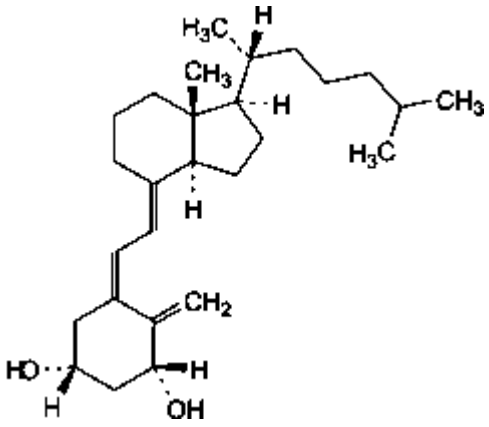
https://thuocngocanh.com/

Specified impurities A, B, D.

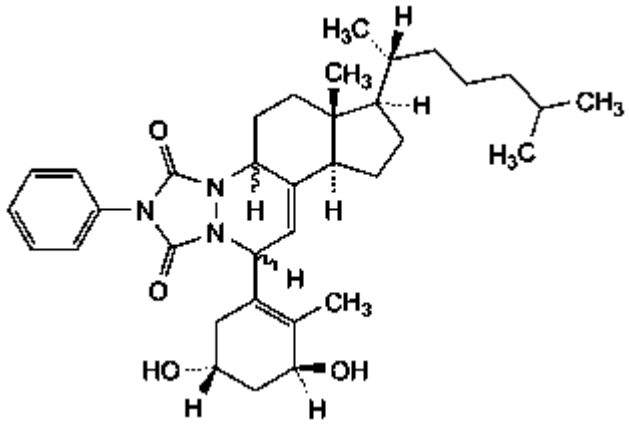
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



A. (1*S*,3*R*,5*E*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1,3-diol (*trans*-alfacalcidol),



B. (1*R*,3*R*,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1,3-diol (1β-calcidol),



C. 6ξ-[(3*S*,5*R*)-3,5-dihydroxy-2-methylcyclohex-1-en-1-yl]-17β-[(2*R*)-6-methylheptan-2-yl]-2-phenyl-2,5,10-triaza-4-nor-9ξ-estr-7-ene-1,3-dione,

www.webofpharma.com

https://thuocngocanh.com/

D. unknown structure.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

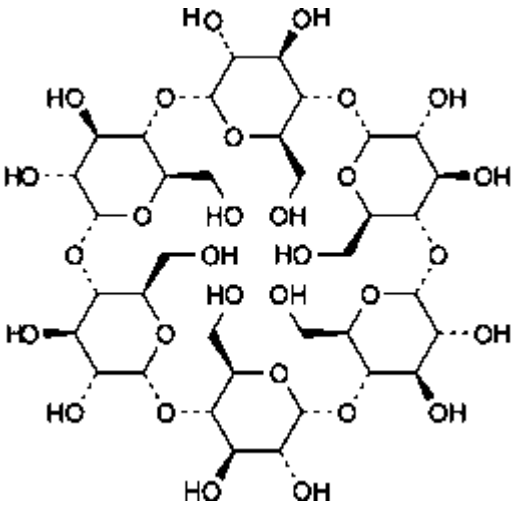
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alfadex

General Notices

Alphacyclodextrin

(Ph. Eur. monograph 1487)



$[C_6H_{10}O_5]_6$ 973 *10016-20-3*

Action and use

Cyclodextran; carrier molecule for drug delivery systems.

Ph Eur

DEFINITION

Cyclohexakis-(1→4)-(α-D-glucopyranosyl) (cyclomaltohexaose or α-cyclodextrin).

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, amorphous or crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, slightly soluble in propylene glycol, practically insoluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Dissolve 0.2 g in 2 mL of *iodine solution R4* by warming on a water-bath, and allow to stand at room temperature; a yellowish-brown precipitate is formed.

TESTS

Solution S

Dissolve 1.000 g in *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*).

pH (*2.2.3*)

5.0 to 8.0.

Mix 1 mL of a 223.6 g/L solution of *potassium chloride R* and 30 mL of solution S.

Specific optical rotation (*2.2.7*)

+ 147 to + 152 (dried substance), determined on solution S.

Reducing sugars

Maximum 0.2 per cent.

Test solution To 1 mL of solution S add 1 mL of *cupri-tartaric solution R4*. Heat on a water-bath for 10 min, cool to room temperature. Add 10 mL of *ammonium molybdate reagent R1* and allow to stand for 15 min.

Reference solution Prepare a reference solution at the same time and in the same manner as the test solution, using 1 mL of a 0.02 g/L solution of *glucose R*.

Measure the absorbance (*2.2.25*) of the test solution and the reference solution at the absorption maximum at 740 nm using *water R* as the compensation liquid. The absorbance of the test solution is not greater than that of the reference solution.

Light-absorbing impurities

www.webofpharma.com

https://thuocngocanh.com/

Examine solution S between 230 nm and 750 nm. Between 230 nm and 350 nm, the absorbance (2.2.25) is not greater than 0.10. Between 350 nm and 750 nm, the absorbance (2.2.25) is not greater than 0.05.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.25 g of the substance to be examined in *water R* with heating, cool and dilute to 25.0 mL with the same solvent.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with *water R*.

Reference solution (a) Dissolve 25.0 mg of *betadex CRS* (impurity A), 25.0 mg of *gammacyclodextrin CRS* (impurity B) and 50.0 mg of *alfadex CRS* in *water R*, then dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with *water R*.

Reference solution (c) Dissolve 25.0 mg of *alfadex CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase *methanol R*, *water R* (10:90 *V/V*).

Flow rate 1.5 mL/min.

Detection Differential refractometer.

Equilibration With the mobile phase for about 3 h.

Injection 50 µL of test solution (a) and reference solutions (a) and (b).

Run time 3.5 times the retention time of alfadex.

Relative retention With reference to alfadex (retention time = about 10 min): impurity B = about 0.7; impurity A = about 2.2.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity B and alfadex; if necessary, adjust the concentration of methanol in the mobile phase.

Limits:

— *impurities A, B*: for each impurity, not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *sum of impurities other than A and B*: not more than 0.5 times the area of the peak due to alfadex in the chromatogram obtained with reference solution (b) (0.5 per cent).

Loss on drying (2.2.32)

Maximum 11 per cent, determined on 1.000 g by drying in an oven at 120 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solutions (a) and (c).

System suitability:

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the peak due to alfadex after 5 injections of reference solution (a).

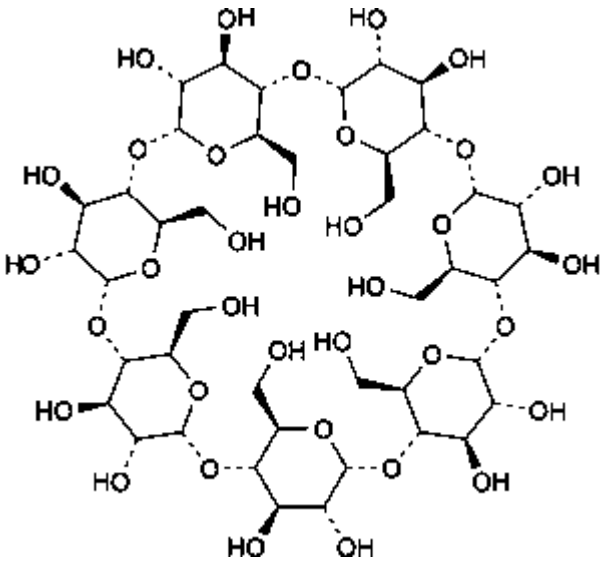
Calculate the percentage content of $[C_6H_{10}O_5]_6$ from the assigned content of *alfadex CRS*.

STORAGE

In an airtight container.

IMPURITIES

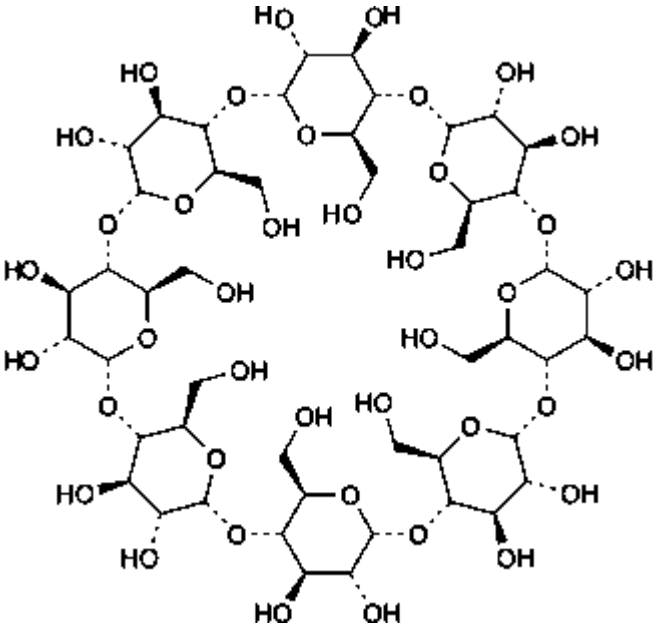
Specified impurities *A, B.*



A. cycloheptakis-(1→4)-(α-D-glucopyranosyl) (betadex or cyclomaltoheptaose or β-cyclodextrin),

www.webofpharma.com

https://thuocngocanh.com/



B. cyclooctakis-(1→4)-(α-D-glucopyranosyl) (cyclomaltooctaose or γ-cyclodextrin).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

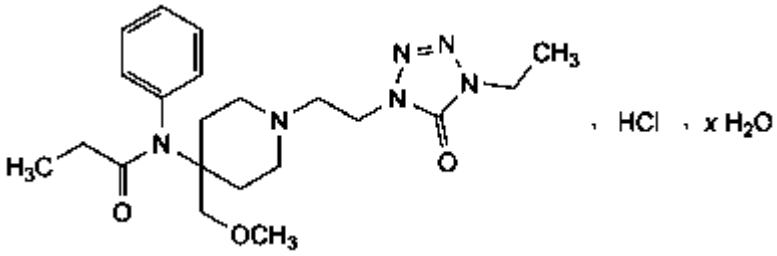
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alfentanil Hydrochloride Hydrate

General Notices

Alfentanil Hydrochloride

(Ph. Eur. monograph 1062)



$C_{21}H_{33}ClN_6O_3$, xH_2O 453.0 (anhydrous substance)

Anhydrous alfentanil hydrochloride *69049-06-5*

Action and use

Opioid receptor agonist; analgesic.

Ph Eur

DEFINITION

N-[1-[2-(4-Ethyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)ethyl]-4-(methoxymethyl)piperidin-4-yl]-*N*-phenylpropanamide hydrochloride hydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, in ethanol (96 per cent) and in methanol.

www.webofpharma.com

https://thuocngocanh.com/

mp

About 140 °C, with decomposition.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *alfentanil hydrochloride hydrate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Dissolve 50 mg in a mixture of 0.4 mL of *ammonia R* and 2 mL of *water R*. Mix, allow to stand for 5 min and filter. Acidify the filtrate with *dilute nitric acid R*. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.2 g in *water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) In order to prepare impurity E *in situ*, dissolve 10 mg of the substance to be examined in 10.0 mL of *dilute hydrochloric acid R*. Heat on a water-bath under a reflux condenser for 4 h. Neutralise with 10.0 mL of *dilute sodium hydroxide solution R* and evaporate to dryness on a water-bath. Cool and take up the residue in 10 mL of *methanol R*. Filter.

Reference solution (b) Dissolve the contents of a vial of *alfentanil impurity D CRS* in 1 mL of *methanol R*.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Blank solution *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: 5 g/L solution of *ammonium carbonate R* in a mixture of 10 volumes of *tetrahydrofuran R* and 90 volumes of *water for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	90 → 40	10 → 60
15 - 20	40	60
20 - 25	40 → 90	60 → 10

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to alfentanil (retention time = about 8 min): impurity D = about 0.8; impurity E = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity E and alfentanil.

Calculation of percentage contents:

— for each impurity, use the concentration of alfentanil hydrochloride hydrate in reference solution (c).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

3.0 per cent to 4.0 per cent, determined on 0.500 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.350 g in 50 mL of a mixture of 1 volume of *ethanol (96 per cent) R* and 4 volumes of *water R* and add 5.0 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 45.30 mg of $C_{21}H_{33}ClN_6O_3$.

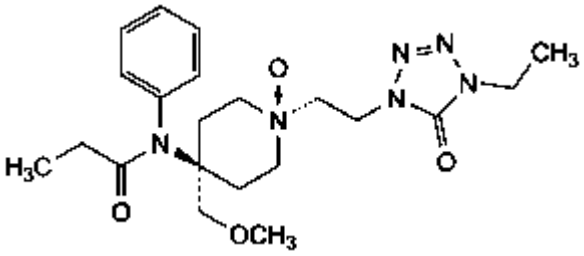
STORAGE

Protected from light.

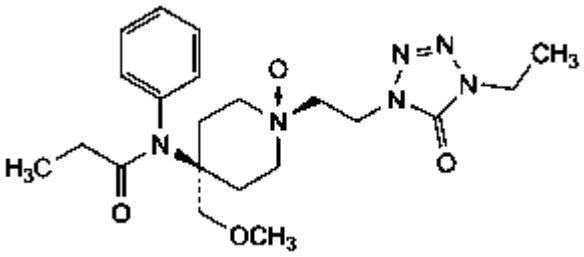
IMPURITIES

Specified impurities D.

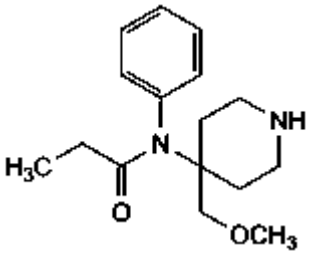
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, E, F, G, H.



A. (1*s*,4*s*)-1-[2-(4-ethyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-(*N*-phenylpropanamido)piperidine 1-oxide,



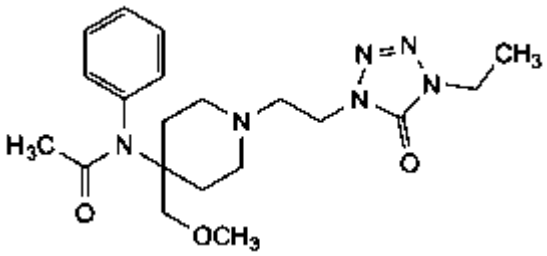
B. (1*r*,4*r*)-1-[2-(4-ethyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-(*N*-phenylpropanamido)piperidine 1-oxide,



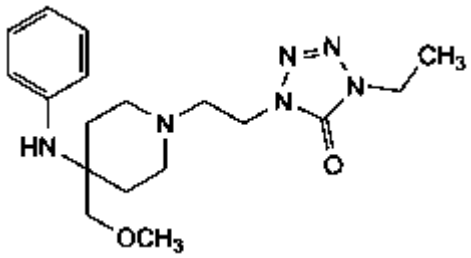
C. *N*-[4-(methoxymethyl)piperidin-4-yl]-*N*-phenylpropanamide,

www.webofpharma.com

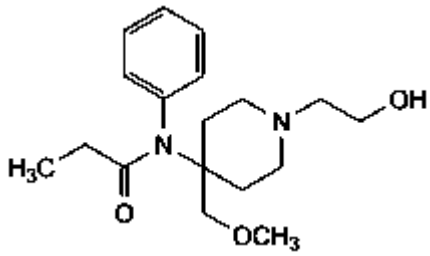
https://thuocngocanh.com/



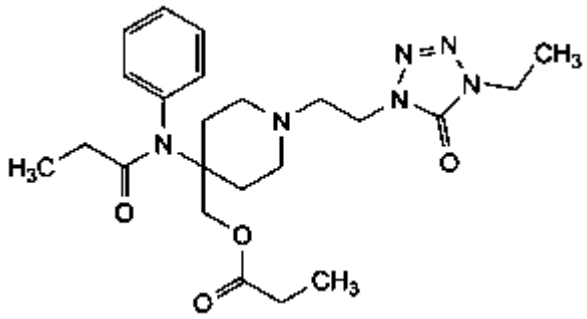
D. *N*-[1-[2-(4-ethyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)ethyl]-4-(methoxymethyl)piperidin-4-yl]-*N*-phenylacetamide,



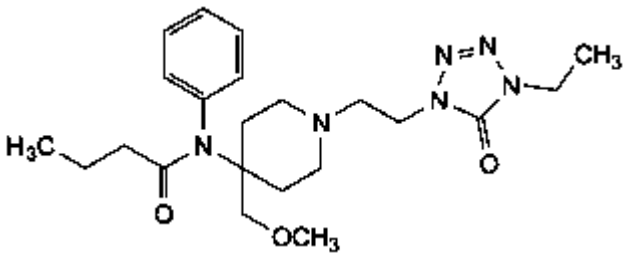
E. 1-ethyl-4-[2-[4-(methoxymethyl)-4-(phenylamino)piperidin-1-yl]ethyl]-1,4-dihydro-5*H*-tetrazol-5-one,



F. *N*-[1-(2-hydroxyethyl)-4-(methoxymethyl)piperidin-4-yl]-*N*-phenylpropanamide,



G. *N*-[1-[2-(4-ethyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)ethyl]-4-[(propanoyloxy)methyl]piperidin-4-yl]-*N*-phenylpropanamide,



H. *N*-[1-[2-(4-ethyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)ethyl]-4-(methoxymethyl)piperidin-4-yl]-*N*-phenylbutanamide.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

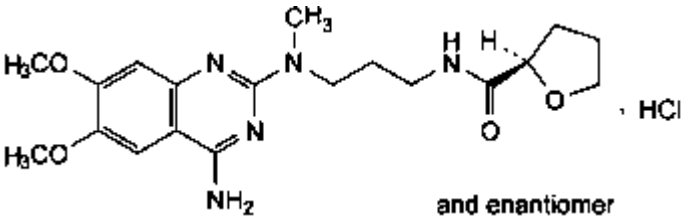
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alfuzosin Hydrochloride

General Notices

(Ph. Eur. monograph 1287)



$C_{19}H_{28}ClN_5O_4$ 425.9 *81403-68-1*

Action and use

Alpha$_1$-adrenoceptor antagonist.

Preparations

Alfuzosin Tablets

Alfuzosin Prolonged-release Tablets

Ph Eur

DEFINITION

(2*RS*)-*N*-[3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]propyl]oxolan-2-carboxamide hydrochloride.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, slightly hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *alfuzosin hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

4.0 to 5.5.

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent. Use a freshly prepared solution.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 40 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of *alfuzosin for system suitability A CRS* (containing impurities B, F and G) in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 4 mg of *alfuzosin for peak identification CRS* (containing impurity D) in the mobile phase and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C; if necessary, increase the temperature slightly to achieve the required resolution between the peaks due to impurity G and alfuzosin.

Mobile phase Mix 1 volume of *tetrahydrofuran R*, 20 volumes of *acetonitrile R* and 80 volumes of a solution prepared as follows: dilute 5.0 mL of *perchloric acid R* in 900 mL of *water for chromatography R*, adjust to pH 3.5 with *dilute sodium hydroxide solution R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

www.webofpharma.com

https://thuocngocanh.com/

Run time Twice the retention time of alfuzosin.

Identification of impurities Use the chromatogram supplied with *alfuzosin for system suitability A CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, F and G; use the chromatogram supplied with *alfuzosin for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to alfuzosin (retention time = about 9 min): impurity D = about 0.4; impurity B = about 0.57; impurity F = about 0.63; impurity G = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and F; minimum 1.5 between the peaks due to impurity G and alfuzosin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 0.6;

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity F*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 40 mL of *anhydrous acetic acid R* and 40 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 42.59 mg of $C_{19}H_{28}ClN_5O_4$.

STORAGE

www.webofpharma.com

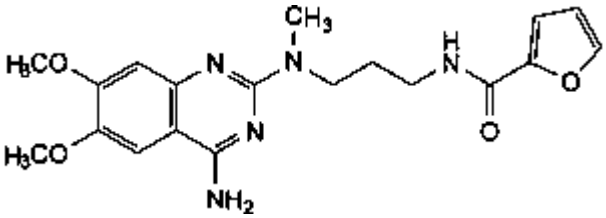
https://thuvienthuocngocanh.com/

In an airtight container, protected from light.

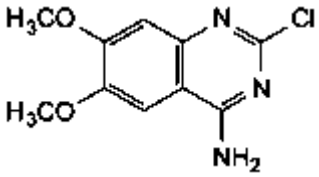
IMPURITIES

Specified impurities *D, F.*

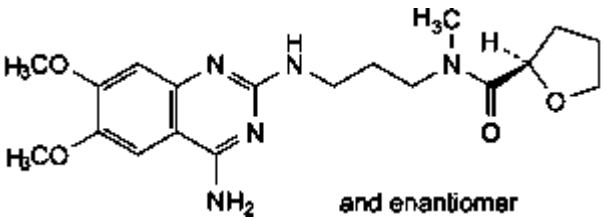
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E, G.*



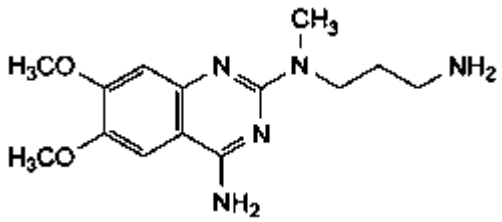
A. *N*-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]propyl]furan-2-carboxamide,



B. 2-chloro-6,7-dimethoxyquinazolin-4-amine,



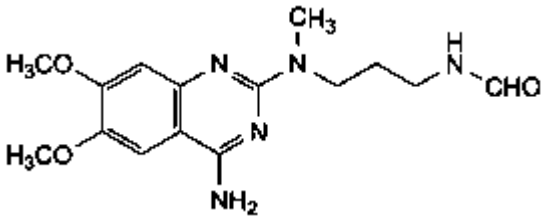
C. (2*RS*)-*N*-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)amino]propyl]-*N*-methyloxolan-2-carboxamide,



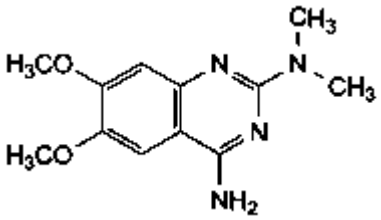
D. N^2-(3-aminopropyl)-6,7-dimethoxy-N^2-methylquinazolin-2,4-diamine,

www.webofpharma.com

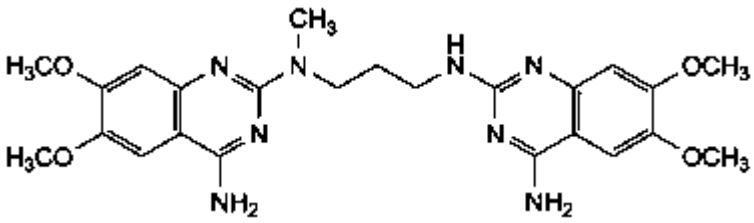
https://thuocngocanh.com/



E. *N*-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]propyl]formamide,



F. 6,7-dimethoxy-N^2,N^2-dimethylquinazoline-2,4-diamine,



G. N^2-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)amino]propyl]-6,7-dimethoxy-N^2-methylquinazoline-2,4-diamine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alfuzosin Prolonged-release Tablets

General Notices

Prolonged-release Alfuzosin Tablets

Alfuzosin Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Alpha$_1$-adrenoceptor antagonist.

DEFINITION

Alfuzosin Prolonged-release Tablets contain Alfuzosin Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of alfuzosin hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of alfuzosin hydrochloride, $C_{19}H_{27}N_5O_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 30 mg of Alfuzosin Hydrochloride with 250 mL of *water* for 5 minutes and filter. Adjust the pH of the filtrate to pH 12.5 with 18M *ammonia*, extract with two 25-mL quantities of *dichloromethane*, wash the combined extracts with 10 mL of *water*, dry over *sodium sulfate* and evaporate to dryness. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of alfuzosin *(RS 446)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of powdered tablets containing 15 mg of Alfuzosin Hydrochloride in 70 mL of *methanol* for 30 minutes, add 10 mL of 0.01M *hydrochloric acid*, cool, dilute to 100 mL with *methanol* and filter. Dilute 1 volume of the solution to 5 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) Dilute 2 volumes of solution (2) to 5 volumes with the mobile phase.

(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

(5) 0.01% w/v of *alfuzosin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

1 volume of *tetrahydrofuran*, 20 volumes of *acetonitrile* and 80 volumes of *sodium perchlorate solution* prepared in the following manner. Add 5 mL of *perchloric acid* to 900 mL of *water*, adjust to pH 3.5 with 2M *sodium hydroxide* and add sufficient *water* to produce 1000 mL.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (5) closely resembles the reference chromatogram supplied with *alfuzosin impurity standard BPCRS*;

the *resolution* between the peaks due to impurity D and impurity E is at least 2.0;

the *resolution* between the peaks due to alfuzosin and impurity A is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D (the first eluting peak in the chromatogram obtained with solution (5)) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E (the second eluting peak in the chromatogram obtained with solution (5)) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any other *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions in the mobile phase.

(1) Weigh and powder 20 tablets. Shake a quantity of powdered tablets containing 10 mg of Alfuzosin Hydrochloride in 70 mL of *methanol* for 30 minutes, add 10 mL of 0.01M *hydrochloric acid*, cool, dilute to 100 mL with *methanol* and filter. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(2) 0.001% w/v of *alfuzosin hydrochloride BPCRS*.

(3) 0.01% w/v of *alfuzosin impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless:

the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *alfuzosin impurity standard BPCRS*;

the *resolution* between the peaks due to impurity D and impurity E is at least 2.0;

the *resolution* between the peaks due to alfuzosin and impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{27}N_5O_4$,HCl in the tablets from the chromatograms obtained and using the declared content of $C_{19}H_{27}N_5O_4$,HCl in *alfuzosin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Alfuzosin Hydrochloride.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuathuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alfuzosin Tablets

General Notices

Action and use

Alpha$_1$-adrenoceptor antagonist.

DEFINITION

Alfuzosin Tablets contain Alfuzosin Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of alfuzosin hydrochloride, $C_{19}H_{27}N_5O_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 30 mg of Alfuzosin Hydrochloride with 50 mL of *water* for 5 minutes and filter. Adjust the pH of the filtrate to 12.5 with 18M *ammonia* extract with two 25-mL quantities of *dichloromethane*, wash the combined extracts with 10 mL of *water*, dry over *sodium sulfate* and evaporate to dryness. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of alfuzosin *(RS 446)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with mobile phase if necessary, to produce a solution expected to contain 0.0001% w/v of Alfuzosin Hydrochloride.

(2) 0.0001% w/v of *alfuzosin hydrochloride BPCRS*.

(3) 0.01% w/v of *alfuzosin impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used. Inject 100 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *alfuzosin impurity standard BPCRS*;

the *resolution* between the peaks due to impurity D and impurity E is at least 2.0;

the *resolution* between the peaks due to alfuzosin and impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of alfuzosin hydrochloride, $C_{19}H_{27}N_5O_4$,HCl, in the medium from the chromatograms obtained and using the declared content of $C_{19}H_{27}N_5O_4$,HCl in *alfuzosin hydrochloride BPCRS*.

LIMITS

The amount of alfuzosin hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 15 mg of Alfuzosin Hydrochloride in 70 mL of *methanol* for 30 minutes, add 10 mL of 0.01M *hydrochloric acid*, cool, dilute to 100 mL with *methanol* and filter. Dilute 1 volume of the solution to 5 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) Dilute 2 volumes of solution (2) to 5 volumes with the mobile phase.

(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

(5) 0.01% w/v of *alfuzosin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

1 volume of *tetrahydrofuran*, 20 volumes of *acetonitrile* and 80 volumes of *sodium perchlorate solution* prepared in the following manner. Add 5 mL of *perchloric acid* to 900 mL of *water*, adjust to pH 3.5 with 2M *sodium hydroxide* and add sufficient *water* to produce 1000 mL.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (5) closely resembles the reference chromatogram supplied with *alfuzosin impurity standard BPCRS*;

the *resolution* between the peaks due to impurity D and impurity E is at least 2.0;

the *resolution* between the peaks due to alfuzosin and impurity A is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D (the first eluting peak in the chromatogram obtained with solution (5)) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E (the second eluting peak in the chromatogram obtained with solution (5)) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Weigh and powder 20 tablets. Shake a quantity of powdered tablets containing 10 mg of Alfuzosin Hydrochloride in 70 mL of *methanol* for 30 minutes, add 10 mL of 0.01M *hydrochloric acid*, cool, dilute to 100 mL with *methanol* and filter. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(2) 0.001% w/v of *alfuzosin hydrochloride BPCRS* in the mobile phase.

(3) 0.01% w/v of *alfuzosin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless:

the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *alfuzosin impurity standard BPCRS*;

www.webofpharma.com

https://thuocngocanh.com/

the *resolution* between the peaks due to impurity D and impurity E is at least 2.0;

the *resolution* between the peaks due to alfuzosin and impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{27}N_5O_4$,HCl in the tablets from the chromatograms obtained and using the declared content of $C_{19}H_{27}N_5O_4$,HCl in *alfuzosin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Alfuzosin Hydrochloride.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alginate Raft-forming Oral Suspension

General Notices

DEFINITION

Alginate Raft-forming Oral Suspension is a suspension containing Sodium Alginate, Sodium Bicarbonate and Calcium Carbonate in a suitable flavoured vehicle. It may be coloured. The suspension forms a raft.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of active constituents

90.0 to 110.0 % of the stated amount of sodium alginate.

PRODUCTION

The content of the active constituents in the oral suspension is measured using suitably validated methods.

IDENTIFICATION

A. Dilute a quantity of the oral suspension containing 0.25 g of Sodium Alginate, accurately weighed, in sufficient *water* to produce 200 mL. Filter and dilute a portion of this solution with sufficient *water* to produce a solution containing 0.0125% w/v of Sodium Alginate. To 1 mL of this solution, add 1 mL of a freshly prepared 4% w/v solution of *resorcinol* and 6 mL of *sulfuric acid*. An orange-pink colour is produced.

B. Evaporate to dryness a quantity of the oral suspension containing 1 g of Sodium Alginate on a water bath. Shake 0.2 g of the residue with 20 mL of *water*. To 5 mL of this solution add 1 mL of *calcium chloride solution*. A voluminous gelatinous mass is formed.

C. Evaporate to dryness a quantity of the oral suspension containing 1 g of Sodium Alginate on a water bath. The residue yields the reactions characteristic of *sodium*, Appendix VI.

TESTS

Alkalinity

pH, 7.0 to 9.5, Appendix V L.

Relative density

1.03 to 1.07 g/mL, Appendix V G.

Raft strength

www.webofpharma.com

https://thuocngocanh.com/

The mean raft strength is not less than 7.5 g, determined by the following method. Carry out the method for *texture analysis of semi-solids or gels*, Appendix XVII F. Introduce 150 mL of *0.1M hydrochloric acid* into a 250 mL beaker having an internal diameter of 60 to 70 mm. Place in a water bath such that the volume of water in the bath is level with the top of the acid in the beaker and allow to equilibrate to 36.5° to 37.5°. Suspend an L-shaped probe comprising 1 mm diameter 316 gauge stainless steel having a 90 mm vertical arm with a hook at the top and a 20 mm horizontal arm such that the vertical arm of the probe hangs down the centre axis of the beaker and the horizontal arm is in the lower third of the acid.

Using a syringe (without needle), remove a quantity of suspension, previously shaken, equivalent to one dose. Where a dosage range is specified, use the maximum dose. Wipe the outside of the syringe and add the suspension evenly into the medium (the time taken to add the entire dose is approximately 5 seconds).

After 30 minutes, remove the beaker from the water bath, dry the outside of the beaker and transfer to a suitable texture analyser. Attach the probe to the arm of the texture analyser, and lift the arm so that the probe is lifted through the raft at a speed of 5 mm/sec. Record the peak raft strength in g.

LABELLING

The label states the sodium content of the suspension.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alginic Acid

General Notices

(Ph. Eur. monograph 0591)

Action and use

Treatment of gastro-oesophageal reflux disease; excipient; thickening agent.

Ph Eur

DEFINITION

Mixture of polyuronic acids $[(C_6H_8O_6)_n]$ composed of residues of D-mannuronic and L-guluronic acids, obtained mainly from algae belonging to the Phaeophyceae. A small proportion of the carboxyl groups may be neutralised.

Content

19.0 per cent to 25.0 per cent of carboxyl groups ($-CO_2H$) (dried substance).

CHARACTERS

Appearance

White or pale yellowish-brown, crystalline or amorphous powder.

Solubility

Very slightly soluble or practically insoluble in ethanol (96 per cent), practically insoluble in organic solvents. It swells in water but does not dissolve; it dissolves in solutions of alkali hydroxides.

IDENTIFICATION

A. To 0.2 g add 20 mL of *water R* and 0.5 mL of *sodium carbonate solution R*. Shake and filter. To 5 mL of the filtrate add 1 mL of *calcium chloride solution R*. A voluminous gelatinous mass is formed.

B. To 5 mL of the filtrate obtained in identification test A add 0.5 mL of a 123 g/L solution of *magnesium sulfate R*. No voluminous gelatinous mass is formed.

C. To 5 mg add 5 mL of *water R*, 1 mL of a freshly prepared 10 g/L solution of *1,3-dihydroxynaphthalene R* in *ethanol (96 per cent) R* and 5 mL of *hydrochloric acid R*. Boil gently for 3 min, cool, add 5 mL of *water R*, and shake with 15 mL of *di-isopropyl ether R*. Carry out a blank test. The upper layer obtained with the substance to be examined exhibits a deeper bluish-red colour than that obtained with the blank.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Chlorides

Maximum 1.0 per cent.

To 2.50 g add 50 mL of *dilute nitric acid R*, shake for 1 h and dilute to 100.0 mL with *dilute nitric acid R*. Filter. To 50.0 mL of the filtrate add 10.0 mL of *0.1 M silver nitrate* and 5 mL of *toluene R*. Titrate with *0.1 M ammonium thiocyanate*, using 2 mL of *ferric ammonium sulfate solution R2* as indicator and shaking vigorously towards the end-point.

1 mL of *0.1 M silver nitrate* is equivalent to 3.545 mg of Cl.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 0.1000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 8.0 per cent (dried substance), determined on 0.100 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

ASSAY

To 0.2500 g add 25 mL of *water R*, 25.0 mL of *0.1 M sodium hydroxide* and 0.2 mL of *phenolphthalein solution R*. Titrate with *0.1 M hydrochloric acid*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 4.502 mg of carboxyl groups ($-CO_2H$).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for alginic acid used as disintegrant and/or binder.

Particle-size distribution (*2.9.31* or *2.9.38*)

www.webofpharma.com

https://thuvienthuocngocanh.com/

Settling volume

Place 75 mL of *water R* in a 100 mL graduated cylinder and add 1.5 g of the substance to be examined in 0.5 g portions, shaking vigorously after each addition. Dilute to 100.0 mL with *water R* and shake again until the substance is homogeneously distributed. Allow to stand for 4 h and determine the volume of the settled mass.

The following characteristic may be relevant for alginic acid used as gelling agent or viscosity-increasing agent.

Apparent viscosity

Determine the dynamic viscosity using a rotating viscometer (*2.2.10*).

Prepare a 20 g/L suspension of alginic acid (dried substance) and add *0.1 M sodium hydroxide* until a solution is obtained.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alimemazine Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Alimemazine Tablets contain Alimemazine Tartrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of alimemazine tartrate, $C_{36}H_{44}N_4S_2,C_4H_6O_6$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 40 mg of Alimemazine Tartrate add 10 mL of *water* and 2 mL of 1M *sodium hydroxide*, shake and extract with 15 mL of *ether*. Wash the ether layer with 5 mL of *water*, dry with *anhydrous sodium sulfate* and evaporate the ether to dryness. Dissolve the residue in 0.4 mL of *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of alimemazine *(RS 005)*.

B. To a quantity of the powdered tablets containing 1 mg of Alimemazine Tartrate add 1 mL of a mixture of equal volumes of *formaldehyde solution* and *sulfuric acid*. A purple colour is produced.

TESTS

Related substances

Comply with the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A* and applying separately to the plate 20 µL of each of the following freshly prepared solutions. For solution (1) extract a quantity of the powdered tablets containing 0.1 g of Alimemazine Tartrate with 10 mL of a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine* and filter. For solution (2) dilute 1 volume of solution (1) to 200 volumes with the same solvent mixture.

ASSAY

Carry out the following procedure protected from light. Add 150 mL of *0.1M hydrochloric acid* to 10 tablets, shake for 10 minutes, mix with the aid of ultrasound for 1 minute, dilute with *0.1M hydrochloric acid* to produce a solution containing 0.050% w/v of Alimemazine Tartrate and filter (solution A). Dilute 10 mL of solution A to 100 mL with *water* (solution B). To a further 10 mL of solution A add 2 mL of *peroxyacetic acid solution*, mix, allow to stand for 5 minutes and add sufficient *water* to produce 100 mL (solution C). Measure the *absorbance* of solution

www.webofpharma.com

https://thuocngocanh.com/

C at the maximum at 342 nm, Appendix II B, using solution B in the reference cell and measure the *absorbance* of solution B at the same wavelength using *water* in the reference cell. Repeat the procedure using a 0.05% w/v solution of *alimemazine tartrate BPCRS* in *0.1M hydrochloric acid* in place of solution A, beginning at the words 'Dilute 10 mL of solution A ...' and calculate the content of $C_{36}H_{44}N_4S_2,C_4H_6O$ using the declared content of $C_{36}H_{44}N_4S_2,C_4H_6O$ in *alimemazine tartrate BPCRS*. The test is not valid if the absorbance of solution B is more than 0.10.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

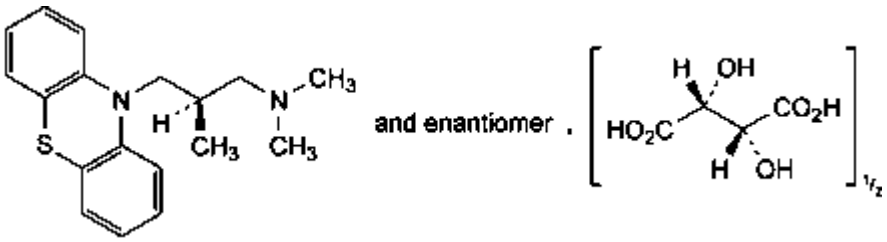
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alimemazine Tartrate

General Notices

(Alimemazine Hemitartrate Ph. Eur. monograph 2650)



$C_{20}H_{25}N_2O_3S$ 373.5 *4330-99-8*

Action and use

Histamine H_1, receptor antagonist; sedative.

Preparations

Paediatric Alimemazine Oral Solution

Strong Paediatric Alimemazine Oral Solution

Alimemazine Tablets

Ph Eur

DEFINITION

(*2RS*)-*N,N,*2-Trimethyl-3-(10*H*-phenothiazin-10-yl)propan-1-amine hemi[(2*R*,3*R*)-2,3-dihydroxybutanedioate].

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or very slightly yellowish powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in toluene.

It deteriorates when exposed to air and light.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *alimemazine hemitartrate CRS*.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

Dissolve 1.0 g in *water R* and dilute to 10 mL with the same solvent.

pH (2.2.3)

5.0 to 6.5. *Carry out the test protected from light and use a freshly prepared solution.*

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and use freshly prepared solutions.*

Solvent mixture *acetonitrile R*, *water R* (20:80 *V/V*).

Test solution Dissolve 35 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 3.5 mg of *alimemazine for system suitability CRS* (containing impurities A, B and C) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, *methanol R*, 3.854 g/L solution of *ammonium acetate R* (10:40:50 *V/V/V*).

Flow rate 1.3 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 253 nm.

Injection 20 µL.

Run time Twice the retention time of alimemazine.

Identification of impurities Use the chromatogram supplied with *alimemazine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to alimemazine (retention time = about 27 min): impurity A = about 0.1; impurity B = about 0.5; impurity C = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to alimemazine and impurity C.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 4.4; impurity C = 0.4;

— for each impurity, use the concentration of alimemazine hemitartrate in reference solution (a).

Limits:

— *impurity B*: maximum 0.3 per cent;

— *impurities A, C*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 37.35 mg of $C_{20}H_{25}N_2O_3S$.

www.webofpharma.com

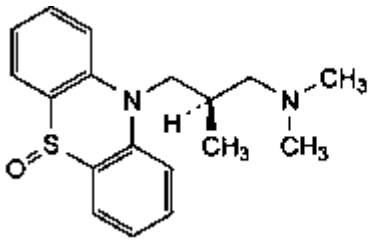
https://thuocngocanh.com/

STORAGE

In an airtight container, protected from light.

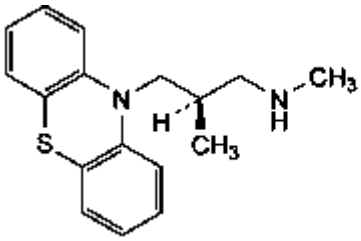
IMPURITIES

Specified impurities *A, B, C.*



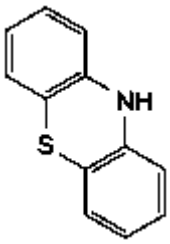
and enantiomer

A. (2*RS*)-*N*,*N*,2-trimethyl-3-(5-oxido-10*H*-phenothiazin-10-yl)propan-1-amine,



and enantiomer

B. (2*RS*)-*N*,2-dimethyl-3-(10*H*-phenothiazin-10-yl)propan-1-amine,



C. 10*H*-phenothiazine.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

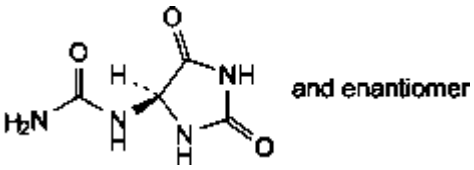
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Allantoin

General Notices

(Ph. Eur. monograph 1288)



$C_4H_6N_4O_3$ 158.1 *97-59-6*

Action and use

Astringent; keratolytic.

Ph Eur

DEFINITION

Allantoin contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (*RS*)-(2,5-dioxoimidazolidin-4-yl)urea.

CHARACTERS

A white or almost white, crystalline powder, slightly soluble in water, very slightly soluble in ethanol (96 per cent).

It melts at about 225 °C, with decomposition.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *allantoin CRS*.

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Boil 20 mg with a mixture of 1 mL of *dilute sodium hydroxide solution R* and 1 mL of *water R*. Allow to cool. Add 1 mL of *dilute hydrochloric acid R*. To 0.1 mL of the solution add 0.1 mL of a 100 g/L solution of *potassium bromide R*, 0.1 mL of a 20 g/L solution of

www.webofpharma.com

https://thuocngocanh.com/

resorcinol R and 3 mL of *sulfuric acid R*. Heat for 5 min to 10 min on a water-bath. A dark blue colour develops, which becomes red after cooling and pouring into about 10 mL of *water R*.

D. Heat about 0.5 g. Ammonia vapour is evolved, which turns *red litmus paper R* blue.

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R*, with heating if necessary, and dilute to 100 mL with the same solvent.

Acidity or alkalinity

To 5 mL of solution S add 5 mL of *carbon dioxide-free water R*, 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Optical rotation (*2.2.7*)

The angle of optical rotation, determined on solution S, is -0.10° to + 0.10°.

Reducing substances

Shake 1.0 g with 10 mL of *water R* for 2 min. Filter. Add 1.5 mL of *0.02 M potassium permanganate*. The solution must remain violet for at least 10 min.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a suitable *cellulose for chromatography R* as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in 5.0 mL of *water R* with heating. Allow to cool. Dilute to 10 mL with *methanol R*. *Use the solution immediately after preparation.*

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with a mixture of 1 volume of *methanol R* and 1 volume of *water R*.

Reference solution (a) Dissolve 10 mg of *allantoin CRS* in a mixture of 1 volume of *methanol R* and 1 volume of *water R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (b) Dissolve 10 mg of *urea R* in 10 mL of *water R*. Dilute 1 mL of this solution to 10 mL with *methanol R*.

Reference solution (c) Mix 1 mL of reference solution (a) and 1 mL of reference solution (b).

Apply to the plate 10 µL of test solution (a) and 5 µL each of test solution (b), reference solution (a), reference solution (b) and reference solution (c). Develop over a path of 10 cm using a mixture of 15 volumes of *glacial acetic acid R*, 25 volumes of *water R* and 60 volumes of *butanol R*. Allow the plate to dry in air. Spray the plate with a 5 g/L solution of *dimethylaminobenzaldehyde R* in a mixture of 1 volume of *hydrochloric acid R* and 3 volumes of *methanol R*. Dry the plate in a current of hot air. Examine in daylight after 30 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated principal spots.

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Not more than 0.1 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

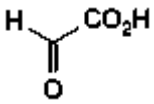
Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

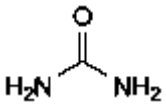
Dissolve 120.0 mg in 40 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 15.81 mg of $C_4H_6N_4O_3$.

IMPURITIES



A. glyoxylic acid,



B. carbamide (urea).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Allergen Products

General Notices

(Ph. Eur. monograph 1063)

Ph Eur

This monograph does not apply to: chemicals that are used solely for diagnosis of contact dermatitis; chemically synthesised products; allergens derived by recombinant DNA technology. It does not necessarily apply to allergen products for veterinary use.

DEFINITION

Allergen products are pharmaceutical preparations derived from extracts of naturally occurring source materials containing allergens, which are substances that lead to and/or provoke allergic reactions. The allergenic components are most often of a proteinaceous nature. Allergen products are intended for *in vivo* diagnosis or treatment of allergic diseases attributed to these allergens.

Allergen products are available as finished products, and as finished products used on a named-patient basis. Allergen products are generally presented as parenteral preparations, eye preparations, preparations for inhalation, preparations for oral use, sublingual preparations or preparations for skin tests.

For *in vivo* diagnostic use, allergen products are usually prepared as unmodified extracts in a 50 per cent *V/V* solution of glycerol for skin testing. For intradermal diagnosis or for provocation tests by nasal, ocular or bronchial administration, suitable dilutions of allergen products may be prepared by dilution of aqueous or glycerinated extracts, or by reconstitution of unmodified freeze-dried extracts.

For *specific immunotherapy*, allergen products may be either unmodified extracts or extracts modified chemically and/or by adsorption onto different carriers (for example, aluminium hydroxide, calcium phosphate or tyrosine).

PRODUCTION

Where allergen products or source materials are manufactured using materials of human or animal origin, the requirements of general chapter *5.1.7. Viral safety* apply.

SOURCE MATERIALS

Source materials are obtained from qualified suppliers. The source materials comply with the requirements of the appropriate individual monographs (where a relevant monograph exists) and the statements in this section are intended to be read in conjunction with the individual monographs.

Source materials for the preparation of allergen products are products of animal or vegetable origin, mostly pollens, moulds, mites, animal epithelia and outgrowths, and Hymenoptera venoms. Other source materials include certain insects and foods.

www.webofpharma.com

https://thuvienthuocngocanh.com/

The source materials are defined, where possible, by their origin, nature, method of collection or production and pretreatment. Control methods and acceptance criteria relating to identity and purity are established. The acceptance criteria must ensure the consistency of the allergenic source material from a qualitative and quantitative point of view. The source materials are stored under controlled conditions justified by stability data.

The collection or production as well as the handling of the source materials are such that consistent composition is ensured from batch to batch.

When applicable, pesticides, heavy metals and residual solvents are limited according to the principles defined in general chapters *2.8.13. Pesticide residues*, *2.4.27. Heavy metals in herbal drugs and herbal drug preparations* and *2.4.24. Identification and control of residual solvents*, respectively.

Microbial contamination of the source material may be unavoidable and should be monitored according to a justified sampling plan; if a determination of microbial contamination is not applicable, this must be justified.

The scientific name (species, variety, strain etc.) of the source material is indicated and the part used is stated, if applicable.

Foods must be of a quality suitable for human consumption. The origin of the food stuff as well as its processing stage are stated.

MANUFACTURING PROCESS

Allergen products are generally obtained by extraction, and may be purified, from the source materials using appropriate methods shown to preserve the allergenic properties of the components. For allergens for which there are not enough patients to determine the total allergenic activity *in vivo* or *in vitro*, the extraction ratio indicating the relative proportions (*m/V*) of allergenic source materials and solvents is a minimum requirement. Allergen products presented as parenteral preparations, eye preparations, preparations for inhalation and preparations for skin testing are manufactured under aseptic conditions.

In the manufacture, packaging, storage and distribution of allergen products intended for administration by other routes, suitable measures are taken to ensure their microbiological quality; recommendations on this aspect are provided in general chapter *5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use*.

All allergen preparations are manufactured under conditions designed to minimise exogenous and endogenous enzymatic degradation.

Any purification procedure is designed to minimise the content of any potential irritant low-molecular-mass components and non-allergenic components.

Allergen products may contain suitable antimicrobial preservatives. The nature and concentration of the antimicrobial preservatives have to be justified and their efficacy complies with general chapter *5.1.3. Efficacy of antimicrobial preservation*.

The manufacturing process comprises various stages:

— source material;

— active substance: it is generally a modified or an unmodified allergen extract; where applicable it is stored under conditions ensuring its stability, for example freeze-dried;

www.webofpharma.com

https://thuocngocanh.com/

— finished product.

All other stages of the manufacturing process are considered as intermediates.

IN-HOUSE REFERENCE PREPARATION

An appropriate representative preparation is selected as the in-house reference preparation (IHRP), characterised and used to verify batch-to-batch consistency. The IHRP is stored in suitably sized aliquots under conditions ensuring its stability, for example freeze-dried.

Characterisation of the in-house reference preparation

The extent of characterisation of the IHRP depends on the source material, knowledge of the allergenic components and availability of suitable reagents, as well as the intended use. The characterised IHRP is used as the reference in the batch control of active substances and intermediates and, if possible, in the batch control of finished products.

The IHRP is characterised by the protein content determination and a protein profile using appropriate methods (such as isoelectric focusing, sodium dodecyl sulfate polyacrylamide gel electrophoresis, immunoelectrophoresis, capillary electrophoresis, chromatographic techniques and mass spectrometry).

Allergenic components may be detected by appropriate methods (for example, immunoblotting or crossed radio-immunoelectrophoresis). Characterisation of the allergenic components may include identification of relevant allergens based on serological or other techniques using pooled or individual sera from allergic patients, or allergen-specific polyclonal or monoclonal antibodies.

Determination of the content of relevant allergens is performed wherever possible. This determination may be made using individual allergen-specific reference standards, when available. The choice of the relevant allergen components subjected to the determination must be justified. Individual allergens are identified and named according to internationally established nomenclature wherever possible.

The biological potency of the first IHRP is determined using a suitable *in vitro* (e.g. inhibition of the binding capacity of specific immunoglobulin E) or *in vivo* method (e.g. skin testing) expressed in units of biological activity. Subsequently, the biological activity of future IHRPs is demonstrated by *in vitro* methods by comparison with the results obtained with the first IHRP.

IDENTIFICATION

The tests for identification are performed as late as possible in the manufacturing process. In the case of products used on a named-patient basis, the control is performed on the active substance and/or at the intermediate stage between the active substance and the finished product.

Identity is confirmed by comparison with the IHRP using protein profiling by appropriate methods (for example, isoelectric focusing, sodium dodecyl sulfate polyacrylamide gel electrophoresis, immunoelectrophoresis, immunoblotting, liquid chromatography or mass spectrometry).

In exceptional cases, if no IHRP is available, a representative batch may be used to confirm identity.

Identity may also be confirmed by comparison with individual allergen-specific reference standards, when available.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

The tests are performed as late as possible in the manufacturing process. In the case of products used on a named-patient basis, the control is performed on the active substance and/or at the intermediate stage between the active substance and the finished product.

Various biochemical and immunological tests have been developed in order to characterise allergens qualitatively and quantitatively. In those cases where such methods cannot be applied, particularly for the determination of allergenic activity and allergen and/or protein profile, justification must be provided.

Water (*2.5.12* or *2.5.32*) or **loss on drying** (*2.2.32*)

Maximum 5 per cent for freeze-dried products. In the case of oral lyophilisates, the water content may be higher than 5 per cent, where justified and authorised.

Sterility (*2.6.1*)

Allergen products presented as parenteral preparations, eye preparations, preparations for inhalation or preparations for skin testing comply with the test.

Microbial contamination

For non-sterile allergen products, recommendations are provided in general chapter *5.1.4*. *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use*.

Protein content (*2.5.33*)

80 per cent to 120 per cent of the stated content, unless otherwise justified and authorised. If the biological potency can be determined, the protein content is within 50 per cent to 150 per cent of the stated content. When the finished product contains proteinaceous excipients, the test for protein content is performed as late as possible during production before addition of the proteinaceous excipient.

Protein profile

The protein profile determined by suitable methods corresponds to that of the IHRP. The presence of relevant allergen components is verified, where possible. The choice of relevant allergen components to be tested for must be justified.

Various additional tests, some with increasing selectivity, depending on the allergen product concerned can be applied, but in any case for allergen products intended for therapeutic use, a validated test measuring the potency (total allergenic activity, determination of individual allergens or any other justified tests) must be applied.

Aluminium (*2.5.13*)

80 per cent to 120 per cent of the stated amount unless otherwise justified and authorised but in any case not more than 1.25 mg per human dose, when aluminium hydroxide or aluminium phosphate is used as adsorbent.

Calcium (*2.5.14*)

80 per cent to 120 per cent of the stated amount when calcium phosphate is used as adsorbent.

Allergen profile

www.webofpharma.com

https://thuvienthuocngocanh.com/

Relevant allergenic components are identified by means of suitable techniques using allergen-specific human or animal antibodies.

Total allergenic activity

50 per cent to 150 per cent of the stated amount as assayed by inhibition of the binding capacity of specific immunoglobulin E antibodies or a suitable equivalent *in vitro* method.

Individual allergens

50 per cent to 200 per cent of the stated amount of each relevant allergen component, determined by a suitable method.

STORAGE

Adsorbed allergen products are not to be frozen, unless otherwise justified and authorised.

LABELLING

The label states:

— the name of the allergen product;

— the biological potency and/or the protein content and/or the extraction concentration;

— the route of administration and the intended use;

— the storage conditions;

— where applicable, the name and amount of added antimicrobial preservative;

— where applicable, for freeze-dried preparations:

— the name, composition and volume of the reconstituting liquid to be added;

— the period of time within which the preparation is to be used after reconstitution;

— where applicable, that the preparation is sterile;

— where applicable, the name and amount of adsorbent.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

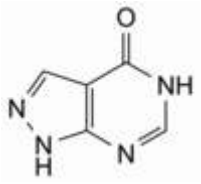
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Allopurinol

General Notices

(Ph. Eur. monograph 0576)



$C_5H_4N_4O$ 136.1 *315-30-0*

Action and use

Xanthine oxidase inhibitor; treatment of gout and hyperuricaemia.

Preparations

Allopurinol Oral Suspension

Allopurinol Tablets

Ph Eur

DEFINITION

1,5-Dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water and in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 10 mg in 1 mL of a 4 g/L solution of *sodium hydroxide R* and dilute to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*. Dilute 10.0 mL of this solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Spectral range 220-350 nm.

Absorption maximum At 250 nm.

Absorption minimum At 231 nm.

Absorbance ratio A_{231}/A_{250} = 0.52 to 0.62.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *allopurinol CRS*.

C. Dissolve 0.3 g in 2.5 mL of *dilute sodium hydroxide solution R* and add 50 mL of *water R*. Add slowly and with shaking 5 mL of *silver nitrate solution R1*. A white precipitate is formed which does not dissolve on the addition of 5 mL of *ammonia R*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *concentrated ammonia R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *allopurinol CRS* in *concentrated ammonia R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous ethanol R*, *methylene chloride R* (40:60 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (2.2.29). *Use freshly prepared solutions. Store and inject them at 8 °C, using a cooled autosampler.*

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 2.5 mL of a 4 g/L solution of *sodium hydroxide R* and dilute immediately to 50.0 mL with the mobile phase.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in 5.0 mL of a 4 g/L solution of *sodium hydroxide R* and dilute immediately to 250.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *allopurinol impurity A CRS*, 5 mg of *allopurinol impurity B CRS* and 5.0 mg of *allopurinol impurity C CRS* in 5.0 mL of a 4 g/L solution of *sodium hydroxide R* and dilute immediately to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 20.0 mg of *allopurinol CRS* in 5.0 mL of a 4 g/L solution of *sodium hydroxide R* and dilute immediately to 250.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 1.25 g/L solution of *potassium dihydrogen phosphate R*.

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time Twice the retention time of allopurinol.

Elution order Impurity A, impurity B, impurity C, allopurinol.

Retention time Allopurinol = about 10 min.

System suitability Reference solution (b):

— *resolution*: minimum 1.1 between the peaks due to impurities B and C.

Limits:

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than A, B and C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurities D and E

Liquid chromatography (2.2.29). *Use freshly prepared solutions. Store and inject them at 8 °C, using a cooled autosampler.*

Solution A 1.25 g/L solution of *potassium dihydrogen phosphate R*.

Test solution Dissolve 50.0 mg of the substance to be examined in 5.0 mL of a 4 g/L solution of *sodium hydroxide R* and dilute immediately to 100.0 mL with solution A.

Reference solution Dissolve 5.0 mg of *allopurinol impurity D CRS* and 5.0 mg of *allopurinol impurity E CRS* in 5.0 mL of a 4 g/L solution of *sodium hydroxide R* and dilute immediately to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase *methanol R*, 1.25 g/L solution of *potassium dihydrogen phosphate R* (10:90 *V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 1.5 times the retention time of impurity E.

Retention times Impurity D = about 3.6 min; impurity E = about 4.5 min.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to impurities D and E.

Limits:

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent);

— *impurity E*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Impurity F

Liquid chromatography (2.2.29).

Under the following conditions, any hydrazine in the sample reacts with benzaldehyde to give benzaldehyde azine.

Solvent mixture Mix equal volumes of *dilute sodium hydroxide solution R* and *methanol R*.

Solution A Dissolve 2.0 g of *benzaldehyde R* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Prepare immediately before use.

Test solution Dissolve 250.0 mg of the substance to be examined in 5 mL of the solvent mixture. Add 4 mL of solution A, mix and allow to stand for 2.5 h at room temperature. Add 5.0 mL of *hexane R* and shake for 1 min. Allow the layers to separate and use the upper layer.

Reference solution Dissolve 10.0 mg of *hydrazine sulfate R* in the solvent mixture by sonicating for about 2 min and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL to 20.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture. To 5.0 mL of the solution obtained, add 4 mL of solution A, mix and allow to stand for 2.5 h at room temperature. Add 5.0 mL of *hexane R* and shake for 1 min. Allow the layers to separate and use the upper layer.

Blank solution To 5 mL of the solvent mixture add 4 mL of solution A, mix and allow to stand for 2.5 h at room temperature. Add 5.0 mL of *hexane R* and shake for 1 min. Allow the layers to separate and use the upper layer.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *cyanosilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm;

— *temperature*: 30 °C.

Mobile phase *2-propanol R*, *hexane R* (5:95 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 310 nm.

Injection 20 µL.

Relative retention With reference to benzaldehyde (retention time = about 2.8 min): benzaldehyde azine = about 0.8.

System suitability Reference solution:

— *resolution*: minimum 2 between the peaks due to benzaldehyde azine and benzaldehyde;

— *signal-to-noise ratio*: minimum 20 for the peak due to benzaldehyde azine.

Limit:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity F*: the area of the peak due to benzaldehyde azine in the chromatogram obtained with the test solution is not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (10 ppm of hydrazine sulfate equivalent to 2.5 ppm of hydrazine).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

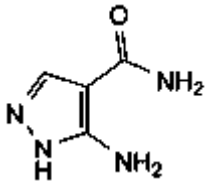
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

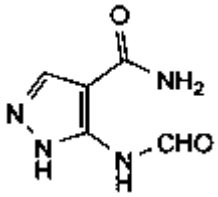
Calculate the percentage content of $C_5H_4N_4O$ from the declared content of *allopurinol CRS*.

IMPURITIES

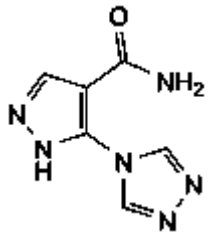
Specified impurities *A, B, C, D, E, F.*



A. 5-amino-1*H*-pyrazole-4-carboxamide,



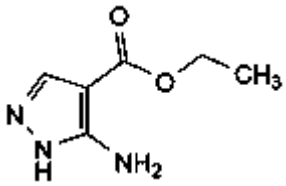
B. 5-(formylamino)-1*H*-pyrazole-4-carboxamide,



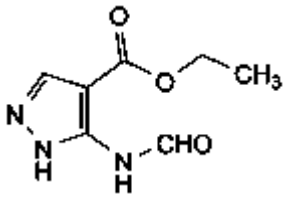
C. 5-(4*H*-1,2,4-triazol-4-yl)-1*H*-pyrazole-4-carboxamide,

www.webofpharma.com

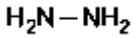
https://thuocngocanh.com/



D. ethyl 5-amino-1*H*-pyrazole-4-carboxylate,



E. ethyl 5-(formylamino)-1*H*-pyrazole-4-carboxylate,



F. diazane (hydrazine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Allopurinol Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Xanthine oxidase inhibitor; treatment of gout and hyperuricaemia.

DEFINITION

Allopurinol Oral Suspension is a suspension of Allopurinol in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of allopurinol, $C_5H_4N_4O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of solution (2) obtained in the Assay is concordant with that of solution (3).

B. In the Assay, the principal peak in the chromatogram obtained with solution (2) has the same retention time as that in the chromatogram obtained with solution (3).

TESTS

Acidity

pH, 2.5 to 4.5, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions, using 900 mL of 0.01M *hydrochloric acid* as the dissolution medium and rotating the paddle at 75 revolutions per minute. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.92% w/v solution of *sulfanilamide* in *methanol* (internal standard solution).

www.webofpharma.com

https://thuocngocanh.com/

(2) To a quantity of the oral suspension containing 0.1 g of Allopurinol add 30 mL of a solution containing 10% w/v of *sodium chloride* in 0.1M *sodium hydroxide*. Add 10 mL of the internal standard solution and sufficient *methanol* to produce 100 mL; mix and filter through glass wool. Dilute 25 volumes of the resulting solution to 100 volumes with a 1% w/v solution of *anhydrous potassium dihydrogen orthophosphate*, mix and filter through a 0.45-µm membrane filter.

(3) Dissolve 0.1 g of *allopurinol BPCRS* in 30 mL of a solution containing 10% w/v of *sodium chloride* in 0.1M *sodium hydroxide*. Add 10 mL of the internal standard solution and sufficient *methanol* to produce 100 mL; mix. Dilute 25 mL of the resulting solution to 100 mL with a 1% w/v solution of *anhydrous potassium dihydrogen orthophosphate*, mix and filter through a 0.45-µm membrane filter.

(4) Dilute 10 volumes of solution (3) to 100 volumes with the mobile phase; further dilute 10 volumes to 100 volumes and then dilute 5 volumes to 100 volumes with the mobile phase; mix and filter through a 0.45-µm membrane filter.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Develosil RP-aqueous is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 250 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

2 volumes of *methanol* and 98 volumes of a 2% w/v solution of *anhydrous potassium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The chromatogram obtained with solution (3) shows a peak due to allopurinol (retention time about 11 minutes) and a peak with a retention relative to allopurinol of about 0.5 (sulfanilamide).

LIMITS

Using the chromatogram obtained with solution (4), calculate the ratio of the area of the peak due to allopurinol to the area of the peak due to the internal standard (*R*).

In the chromatogram obtained with solution (2):

the ratio of the area of any *secondary peak* to the area of the peak due to the internal standard is not greater than 0.04*R* (0.2%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.92% w/v solution of *sulfanilamide* in *methanol* (internal standard solution).

(2) To a weighed quantity of the oral suspension containing 0.1 g of Allopurinol add 30 mL of a solution containing 10% w/v of *sodium chloride* in 0.1M *sodium hydroxide*. Add 10 mL of the internal standard solution and sufficient *methanol* to produce 100 mL; mix and filter through glass wool. Dilute 25 volumes of the resulting solution to 100 volumes with a 1% w/v solution of *anhydrous potassium dihydrogen orthophosphate*, mix and filter through a 0.45-µm membrane filter.

www.webofpharma.com

https://thuocngocanh.com/

(3) Dissolve 0.1 g of *allopurinol BPCRS* in 30 mL of a solution containing 10% w/v of *sodium chloride* in 0.1M *sodium hydroxide*. Add 10 mL of the internal standard solution and sufficient *methanol* to produce 100 mL; mix. Dilute 25 volumes of the resulting solution to 100 volumes with a 1% w/v solution of *anhydrous potassium dihydrogen orthophosphate*, mix and filter through a 0.45-µm membrane filter.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Develosil RP-aqueous is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 250 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

2 volumes of *methanol* and 98 volumes of a 2% w/v solution of *anhydrous potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_5H_4N_4O$, weight in volume, using the declared content of $C_5H_4N_4O$ in *allopurinol BPCRS*.

Impurities

The impurities limited by the requirements of this monograph include impurities A, B, C, D and E listed under Allopurinol.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Allopurinol Tablets

General Notices

Action and use

Xanthine oxidase inhibitor; treatment of gout and hyperuricaemia.

DEFINITION

Allopurinol Tablets contain Allopurinol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of allopurinol, $C_5H_4N_4O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution obtained in the Assay exhibits a maximum only at 250 nm.

B. Shake a quantity of the powdered tablets containing 0.1 g of Allopurinol with 5 mL of 1.25M *sodium hydroxide* and add 3 mL of *phosphomolybdotungstic reagent* and 5 mL of a 20% w/v solution of *sodium carbonate*. A greyish blue colour is produced.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Allopurinol with 10 mL of 0.1M *sodium hydroxide* for about 1 minute, immediately dilute to 200 mL with mobile phase A and filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A and further dilute 1 volume to 10 volumes with mobile phase A.

(3) Dissolve 10 mg of *allopurinol impurity A BPCRS* and 5 mg each of *allopurinol impurity B BPCRS*, *allopurinol impurity C BPCRS*, *allopurinol impurity D BPCRS* and *allopurinol impurity E BPCRS* in mobile phase A. Add 20 mL of solution (1) and immediately dilute to 100 mL with mobile phase A. Dilute 1 mL of the resulting solution to 100 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 5µ is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A mixture of 1 volume of *methanol* and 9 volumes of a 0.125% w/v solution of *potassium dihydrogen orthophosphate*.

Mobile phase B A mixture of 3 volumes of *methanol* with 7 volumes of a 0.125% w/v solution of *potassium dihydrogen orthophosphate*.

Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0-30	100→0	0→100	linear gradient
30-40	0	100	isocratic

SYSTEM SUITABILITY

The test is not valid unless in solution (3) the *resolution factor* between the peaks corresponding to impurity A and allopurinol is at least 3.

Inject solution (3). When the chromatogram is recorded in the prescribed conditions, the retention times are: impurity A, about 4.2 minutes; impurities B and C, about 6.1 minutes; allopurinol, about 7.7 minutes; impurity D, about 26.1 minutes; impurity E, about 27.8 minutes. Inject solution (1) and solution (2). Continue the chromatography of solution (1) for 5 times the retention time of allopurinol.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.2%);

the area of any unresolved double peak corresponding to impurities B and C is not greater than the area of the corresponding double peak in the chromatogram obtained with solution (3) (0.2%);

the area of any peaks corresponding to impurity D or impurity E is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any other *secondary peak* is not greater than the area of the peak due to allopurinol in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 3 times the area of the peak due to allopurinol in the chromatogram obtained with solution (2) (0.3%).

Disregard any peak with an area less than 0.2 times that of the peak due to allopurinol in the chromatogram obtained with solution (2) (0.02%).

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of Allopurinol with 20 mL of 0.05M *sodium hydroxide* for 20 minutes, add 80 mL of 0.1M *hydrochloric acid*, shake for 10 minutes, add sufficient 0.1M *hydrochloric acid* to produce 250 mL, filter and dilute 10 mL of the filtrate to 250 mL with 0.1M *hydrochloric acid*. Measure the *absorbance* of the resulting solution at the maximum at 250 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell. Calculate the content of $C_5H_4N_4O$ taking 563 as the value of A (1%, 1 cm) at the maximum at 250 nm.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

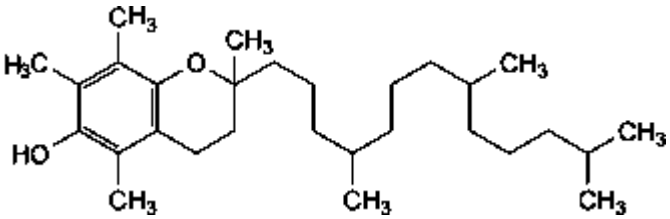
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

all-rac-Alpha-Tocopherol

General Notices

(all-rac-α-Tocopherol, Ph. Eur. monograph 0692)



$C_{29}H_{50}O_2$ 430.7 *10191-41-0*

Action and use

Used in prevention and treatment of vitamin E deficiencies.

Ph Eur

DEFINITION

All-*rac*-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-1-benzopyran-6-ol.

Content

96.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

Clear, colourless or yellowish-brown, viscous, oily liquid.

Solubility

Practically insoluble in water, freely soluble in acetone, in anhydrous ethanol, in methylene chloride and in fatty oils.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Optical rotation (2.2.7): -0.01° to + 0.01°.

Dissolve 2.50 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *α-tocopherol CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 2 mL of *cyclohexane R*.

Reference solution Dissolve 10 mg of *α-tocopherol CRS* in 2 mL of *cyclohexane R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Internal standard solution Dissolve 1.0 g of *squalane R* in *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Test solution (a) Dissolve 0.100 g of the substance to be examined in 10.0 mL of the internal standard solution.

Test solution (b) Dissolve 0.100 g of the substance to be examined in 10 mL of *cyclohexane R*.

Reference solution (a) Dissolve 0.100 g of *α-tocopherol CRS* in 10.0 mL of the internal standard solution.

Reference solution (b) Dissolve 10 mg of the substance to be examined and 10 mg of *α-tocopheryl acetate R* in *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dissolve 10 mg of *all-rac-α-tocopherol for peak identification CRS* (containing impurities A and B) in *cyclohexane R* and dilute to 1 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dilute 1.0 mL of test solution (b) to 100.0 mL with *cyclohexane R*. Dilute 1.0 mL of this solution to 10.0 mL with *cyclohexane R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

— *column*: 280 °C;

— *injection port and detector*: 290 °C.

Detection Flame ionisation.

Injection 1 µL of test solution (b) and reference solutions (b), (c) and (d).

Run time Twice the retention time of all-*rac*-α-tocopherol.

Identification of impurities Use the chromatogram supplied with *all-rac-α-tocopherol for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to all-*rac*-α-tocopherol (retention time = about 9 min): squalane = about 0.5; impurity A = about 0.7; impurity B = about 0.8; impurities C and D = about 1.05 (eluting immediately after the all-*rac*-α-tocopherol peak).

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to all-*rac*-α-tocopherol and α-tocopheryl acetate.

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity B*: maximum 1.5 per cent;

— *sum of impurities C and D*: maximum 1.0 per cent;

— *any other impurity*: for each impurity, maximum 0.25 per cent;

— *total*: maximum 2.5 per cent;

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ASSAY

Gas chromatography (*2.2.28*) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: minimum 0.6 for the principal peak.

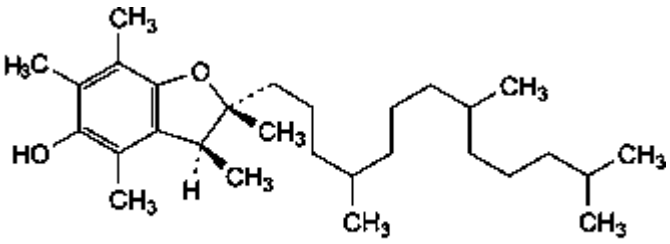
Calculate the percentage content of $C_{29}H_{50}O_2$ from the declared content of *α-tocopherol CRS*.

STORAGE

Under an inert gas, protected from light.

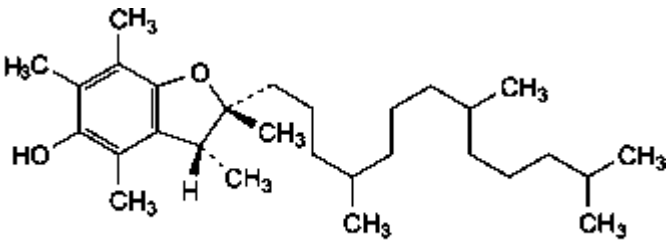
IMPURITIES

Specified impurities *A, B, C, D.*



and diastereoisomers

A. all-*rac-trans*-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-ol,

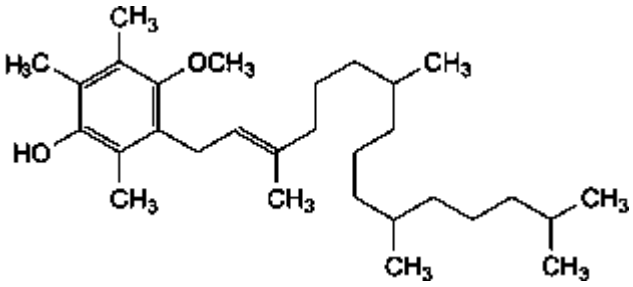


and diastereoisomers

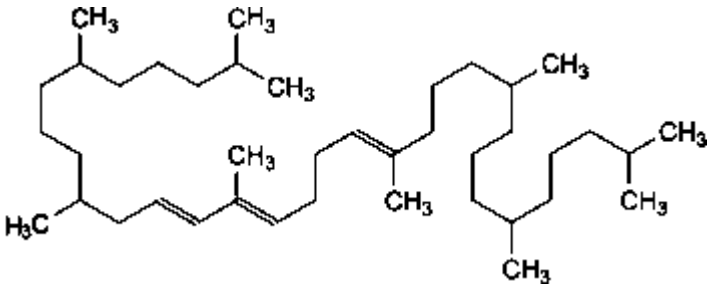
B. all-*rac-cis*-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-ol,

www.webofpharma.com

https://thuocngocanh.com/



C. 4-methoxy-2,3,6-trimethyl-5-[(all-*RS*,*E*)-3,7,11,15-tetramethylhexadec-2-enyl]phenol,



D. (all-*RS*,all-*E*)-2,6,10,14,19,23,27,31-octamethyldotriaconta-12,14,18-triene.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

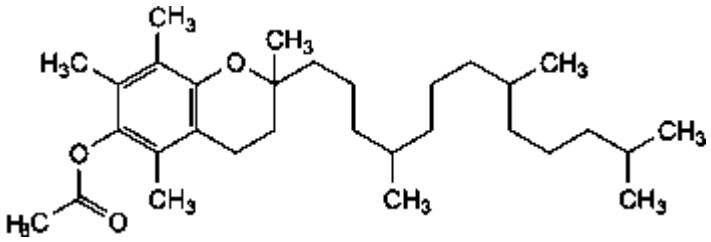
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

all-rac-Alpha-Tocopheryl Acetate

General Notices

(all-rac-α-Tocopheryl Acetate, Ph. Eur. monograph 0439)



$C_{31}H_{52}O_3$ 472.7 *7695-91-2*

Action and use

Used in prevention and treatment of vitamin E deficiencies.

Ph Eur

DEFINITION

all-*rac*-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-1-benzopyran-6-yl acetate.

Content

96.5 per cent to 102.0 per cent.

CHARACTERS

Appearance

Clear, colourless or slightly greenish-yellow, viscous, oily liquid.

Solubility

Practically insoluble in water, freely soluble in acetone, in anhydrous ethanol and in fatty oils.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Optical rotation (2.2.7): -0.01° to + 0.01°.

Dissolve 2.50 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *α-tocopheryl acetate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve about 10 mg of the substance to be examined in 2 mL of *cyclohexane R*.

Reference solution Dissolve about 10 mg of *α-tocopheryl acetate CRS* in 2 mL of *cyclohexane R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ether R*, *cyclohexane R* (20:80 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Internal standard solution Dissolve 1.0 g of *squalane R* in *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Test solution (a) Dissolve 0.100 g of the substance to be examined in 10.0 mL of the internal standard solution.

Test solution (b) Dissolve 0.100 g of the substance to be examined in 10 mL of *cyclohexane R*.

Reference solution (a) Dissolve 0.100 g of *α-tocopheryl acetate CRS* in 10.0 mL of the internal standard solution.

Reference solution (b) Dissolve 10 mg of the substance to be examined and 10 mg of *α-tocopherol R* in *cyclohexane R* and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dissolve 10 mg of *all-rac-α-tocopheryl acetate for peak identification CRS* (containing impurities A and B) in *cyclohexane R* and dilute to 1 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dilute 1.0 mL of test solution (b) to 100.0 mL with *cyclohexane R*. Dilute 1.0 mL of this solution to 10.0 mL with *cyclohexane R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

— *column*: 280 °C;

— *injection port and detector*: 290 °C.

Detection Flame ionisation.

Injection 1 µL of test solution (b) and reference solutions (a), (b), (c) and (d); inject directly onto the column or via a sufficiently inert, glass-lined injection port using an automatic injection device or other reproducible injection method.

Run time Twice the retention time of all-*rac*-α-tocopheryl acetate.

Identification of impurities Use the chromatogram supplied with *all-rac-α-tocopheryl acetate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to all-*rac*-α-tocopheryl acetate (retention time = about 15 min): squalane = about 0.4; impurity A = about 0.7; impurity B = about 0.8; impurity C = about 0.9; impurities D and E = about 1.05 (eluting immediately after the all-*rac*-α-tocopheryl acetate peak).

System suitability:

— *resolution*: minimum 3.5 between the peaks due to impurity C and all-*rac*-α-tocopheryl acetate in the chromatogram obtained with reference solution (b);

— in the chromatogram obtained with reference solution (a), the area of the peak due to impurity C is not greater than 0.2 per cent of the area of the peak due to all-*rac*-α-tocopheryl acetate.

Limits:

— *impurities A, C*: for each impurity, maximum 0.5 per cent;

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *impurity B*: maximum 1.5 per cent;

— *sum of impurities D and E*: maximum 1.0 per cent;

— *any other impurity*: for each impurity, maximum 0.25 per cent;

— *total*: maximum 2.5 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ASSAY

Gas chromatography (*2.2.28*) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: minimum 0.6 for the principal peak.

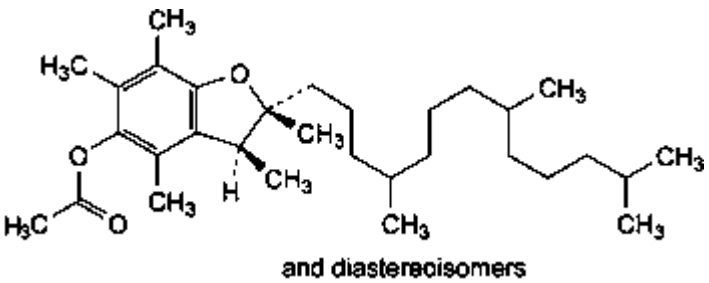
Calculate the percentage content of $C_{31}H_{52}O_3$ from the declared content of *α-tocopheryl acetate CRS*.

STORAGE

Protected from light.

IMPURITIES

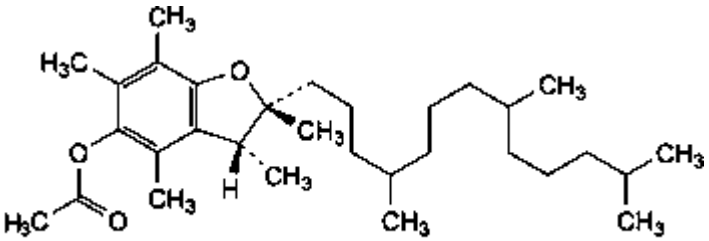
Specified impurities *A, B, C, D, E*.



A. all-*rac-trans*-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-yl acetate,

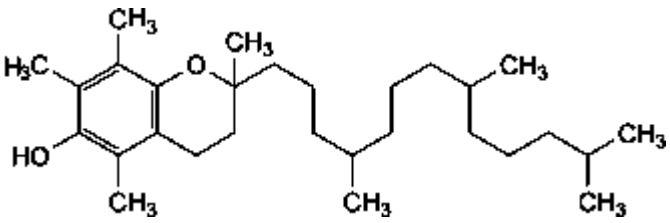
www.webofpharma.com

https://thuvienthuocngocanh.com/

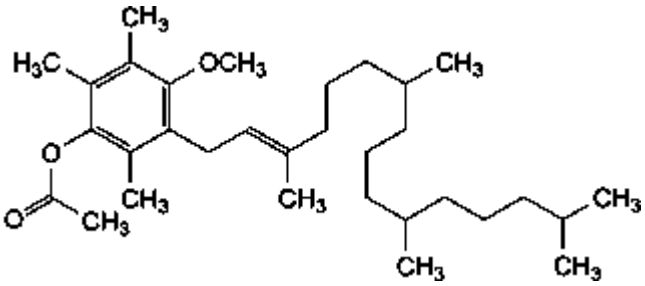


and diastereoisomers

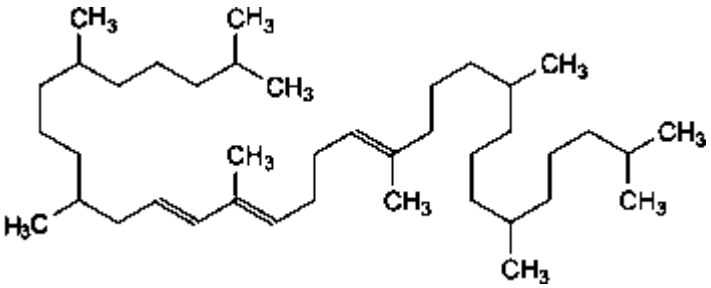
B. all-*rac*-*cis*-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-yl acetate,



C. all-*rac*-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-1-benzopyran-6-ol (all-*rac*-α-tocopherol),



D. 4-methoxy-2,3,6-trimethyl-5-[(all-*RS*,*E*)-3,7,11,15-tetramethylhexadec-2-enyl]phenyl acetate,



E. (all-*RS*,all-*E*)-2,6,10,14,19,23,27,31-octamethyldotriaconta-12,14,18-triene.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Almagate

General Notices

(Ph. Eur. monograph 2010)

$Al_2Mg_6C_2O_{20}H_{14},4H_2O$ 630 *66827-12-1*

Action and use

Antacid.

Ph Eur

DEFINITION

Hydrated aluminium magnesium hydroxycarbonate.

Content

— aluminium: 15.0 per cent to 17.0 per cent (calculated as Al_2O_3),

— magnesium: 36.0 per cent to 40.0 per cent (calculated as MgO),

— carbonic acid: 12.5 per cent to 14.5 per cent (calculated as CO_2).

CHARACTERS

Appearance

White or almost white, fine, crystalline powder.

Solubility

Practically insoluble in water, in ethanol (96 per cent) and in methylene chloride. It dissolves with effervescence and heating in dilute mineral acids.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of almagate*.

B. Dissolve 0.15 g in *dilute hydrochloric acid R* and dilute to 20 mL with the same acid. 2 mL of the solution gives the reaction of aluminium (*2.3.1*).

www.webofpharma.com

https://thuocngocanh.com/

C. 2 mL of the solution prepared under identification test B gives the reaction of magnesium (2.3.1).

TESTS

pH (2.2.3)

9.1 to 9.7.

Disperse 4.0 g in 100 mL of carbon dioxide-free water R, stir for 2 min and filter.

Neutralising capacity

Carry out the test at 37 °C Disperse 0.5 g in 100 mL of water R, heat, add 100.0 mL of 0.1 M hydrochloric acid, previously heated and stir continuously; the pH (2.2.3) of the solution between 5 min and 20 min is not less than 3.0 and not greater than 4.5. Add 10.0 mL of 0.5 M hydrochloric acid, previously heated, stir continuously for 1 h and titrate with 0.1 M sodium hydroxide to pH 3.5; not more than 20.0 mL of 0.1 M sodium hydroxide is required.

Chlorides (2.4.4)

Maximum 0.1 per cent.

Dissolve 0.33 g in 5 mL of dilute nitric acid R and dilute to 100 mL with water R. Prepare simultaneously the standard by diluting 0.7 mL of dilute nitric acid R to 5 mL with water R and adding 10 mL of chloride standard solution (5 ppm Cl) R.

Sulfates (2.4.13)

Maximum 0.4 per cent.

Dissolve 0.25 g in 5 mL of dilute hydrochloric acid R and dilute to 100 mL with distilled water R. Prepare simultaneously the standard by adding 0.8 mL of dilute hydrochloric acid R to 15 mL of sulfate standard solution (10 ppm SO_4) R.

Sodium

Maximum 150 ppm.

Atomic absorption spectrometry (2.2.23, Method I).

Test solution Dissolve 0.25 g in 50 mL of a 103 g/L solution of hydrochloric acid R.

Reference solutions Prepare the reference solutions using sodium standard solution (200 ppm Na) R, diluted as necessary with a 103 g/L solution of hydrochloric acid R.

Loss on ignition

43.0 per cent to 49.0 per cent, determined on 1.000 g by ignition at 900 ± 50 °C.

Microbial contamination

www.webofpharma.com

https://thuocngocanh.com/

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Pseudomonas aeruginosa* (2.6.13).

ASSAY

Aluminium

Dissolve 1.000 g in 5 mL of *hydrochloric acid R*, heating if necessary. Allow to cool to room temperature and dilute to 100.0 mL with *water R* (solution A). Introduce 10.0 mL of solution A into a 250 mL conical flask, add 25.0 mL of *0.05 M sodium edetate*, 20 mL of *buffer solution pH 3.5 R*, 40 mL of *anhydrous ethanol R* and 2 mL of a freshly prepared 0.25 g/L solution of *dithizone R* in *anhydrous ethanol R*. Titrate the excess of sodium edetate with *0.05 M zinc sulfate* until the colour changes from greenish-violet to pink.

1 mL of *0.05 M sodium edetate* is equivalent to 2.549 mg of Al_2O_3.

Magnesium

Introduce 10.0 mL of solution A prepared in the assay of aluminium into a 500 mL conical flask, add 200 mL of *water R*, 20 mL of *triethanolamine R* with shaking, 10 mL of *ammonium chloride buffer solution pH 10.0 R* and 50 mg of *mordant black 11 triturate R*. Titrate with *0.05 M sodium edetate* until the colour changes from violet to pure blue.

1 mL of *0.05 M sodium edetate* is equivalent to 2.015 mg of MgO.

Carbonic acid

12.5 per cent to 14.5 per cent.

Test sample Place 7.00 mg of the substance to be examined in a tin capsule. Seal the capsule.

Reference sample Place 7.00 mg of *almagate CRS* in a tin capsule. Seal the capsule.

Introduce separately the test sample and the reference sample into a combustion chamber of a CHN analyser purged with *helium for chromatography R* and maintained at a temperature of 1020 °C. Simultaneously, introduce *oxygen R* at a pressure of 40 kPa and a flow rate of 20 mL/min and allow complete combustion of the sample. Sweep the combustion gases through a reduction reactor and separate the gases formed by gas chromatography (2.2.28).

Column:

— *size*: *l* = 2 m, Ø = 4 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R*.

Carrier gas *helium for chromatography R*.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 100 mL/min.

Temperature:

— *column*: 65 °C;

— *detector*: 190 °C.

Detection Thermal conductivity.

Run time 16 min.

System suitability:

— average percentage of carbon in 5 reference samples must be within ± 0.2 per cent of the value assigned to the CRS; the difference between the upper and the lower values of the percentage of carbon in these samples must be below 0.2 per cent.

Calculate the percentage content of carbonic acid in the test sample according to the following formula:

$$C \times K \times \frac{A}{m}$$

C	=	percentage content of carbonic acid in the reference sample;
K	=	mean value for the 5 reference samples of the ratio of the mass in milligrams to the area of the peak due to carbonic acid;
A	=	area of the peak due to carbonic acid in the chromatogram obtained with the test sample;
m	=	sample mass, in milligrams.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Almond Oil Ear Drops

General Notices

DEFINITION

Almond Oil Ear Drops are Virgin Almond Oil in a suitable container.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

IDENTIFICATION

Carry out the test for the *identification of fatty oils by thin-layer chromatography*, Appendix X N. The chromatogram obtained from the oil being examined shows spots corresponding to those in the *typical chromatogram* for almond oil.

TESTS

Acid value

Not more than 2.0, Appendix X B. Use 5 g dissolved in 50 mL of the prescribed mixture of solvents.

Peroxide value

Not more than 10, Appendix X F.

Relative density

0.911 to 0.920, Appendix V G.

Unsaponifiable matter

Not more than 0.7% w/w, Appendix X H, Method II. Use 5 g.

Apricot-kernel oil and peach-kernel oil

Shake 2 mL for 5 minutes with a mixture of 1 mL of *fuming nitric acid* and 1 mL of *water* and allow to separate. No pink or brown colour develops in either layer.

Foreign fixed oils

Carry out the test for *composition of fatty acids by gas chromatography*, Appendix X N. The fatty-acid fraction of the oil has the following composition.

Saturated fatty acids of chain length less than C_{16} Not more than 0.1%.

www.webofpharma.com

https://thuocngocanh.com/

Palmitic acid 4.0 to 9.0%.

Palmitoleic acid *(equivalent chain length on polyethylene glycol adipate, 16.3)* Not more than 0.6%.

Margaric acid Not more than 0.2%.

Stearic acid Not more than 3.0%.

Oleic acid *(equivalent chain length on polyethylene glycol adipate, 18.3)* 62.0 to 86.0%.

Linoleic acid *(equivalent chain length on polyethylene glycol adipate, 18.9)* 20.0 to 30.0%.

Linolenic acid *(equivalent chain length on polyethylene glycol adipate, 19.7)* Not more than 0.4%.

Arachidic acid Not more than 0.1%.

Gadoleic acid (equivalent chain length on polyethylene glycol adipate, 20.3) Not more than 0.1%.

Behenic acid Not more than 0.1%.

Erucic acid (equivalent chain length on polyethylene glycol adipate, 22.3) Not more than 0.1%.

Sterols

Carry out the test for *sterols in fatty oils*, Appendix X N. The sterol fraction of the oil has the following composition.

Cholesterol Not more than 0.7%.

Campesterol Not more than 4.0%.

Stigmasterol Not more than 3.0%.

β-*Sitosterol* 73.0% to 87.0%.

Δ^5-*Avenasterol* At least 10.0%.

Δ^7-*Avenasterol* Not more than 3.0%.

Δ^7-*Stigmastenol* Not more than 3.0%.

Fucosterol Not more than 2.0%.

Brassicasterol Not more than 0.3%.

Sesame oil

Shake 10 mL with 5 mL of a mixture of 0.5 volume of a 0.35% v/v solution of *furfuraldehyde* in *acetic anhydride* and 4.5 volumes of *acetic anhydride* for 1 minute, filter through a filter paper impregnated with *acetic anhydride* and add 0.2 mL of *sulfuric acid*. No bluish green colour develops.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

Almond Oil Ear Drops should be kept in a well-filled container and protected from light.

© Crown Copyright 2022

www.webofpharma.com

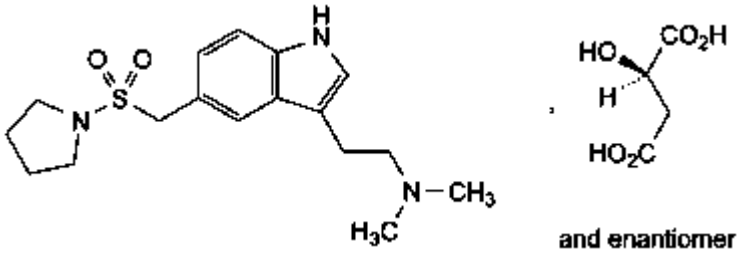
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Almotriptan Malate

General Notices

(Ph Eur. monograph 2970)



and enantiomer

$C_{21}H_{31}N_3O_7S$ 469.6 *181183-52-8*

Action and use

Serotonin 5HT1 receptor agonist; treatment of migraine.

Ph Eur

DEFINITION

N,*N*-Dimethyl-2-[5-[(pyrrolidine-1-sulfonyl)methyl]-1*H*-indol-3-yl]ethan-1-amine (*RS*)-2-hydroxybutanedioate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Soluble in water, slightly soluble in methanol, practically insoluble in anhydrous ethanol and in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *almotriptan malate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture acetonitrile R, water R (20:80 *V/V*).

Buffer solution Dissolve 0.5 g of sodium octanesulfonate monohydrate R in about 900 mL of water for chromatography R. Add 5 mL of phosphoric acid R, adjust to pH 3.0 with sodium hydroxide solution R and dilute to 1000 mL with water for chromatography R.

Test solution (a) Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 25.0 mg of almotriptan malate CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of almotriptan for system suitability CRS (containing impurity A) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: acetonitrile for chromatography R, buffer solution (10:90 *V/V*);

— *mobile phase B*: buffer solution, acetonitrile for chromatography R (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	85	15
5 - 20	85 → 78	15 → 22

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
20 - 30	78 → 70	22 → 30
30 - 40	70	30

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 228 nm.

Injection 5 µL of test solution (a) and reference solutions (a) and (c).

Identification of impurities Use the chromatogram supplied with *almotriptan for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to almotriptan (retention time = about 27 min): malic acid = about 0.1; impurity A = about 0.96.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity A and almotriptan.

Calculation of percentage contents:

— for each impurity, use the concentration of almotriptan malate in reference solution (a).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.7 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to malic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase *acetonitrile for chromatography R*, buffer solution (27:73 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Injection 10 µL of test solution (b) and reference solution (b).

Run time Twice the retention time of almotriptan.

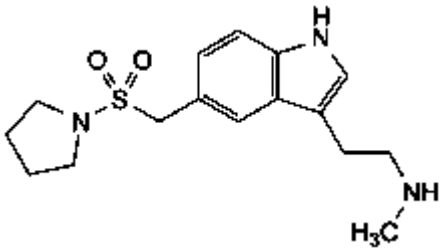
Retention time Almotriptan = about 9 min.

Calculate the percentage content of $C_{21}H_{31}N_3O_7S$ taking into account the assigned content of *almotriptan malate CRS*.

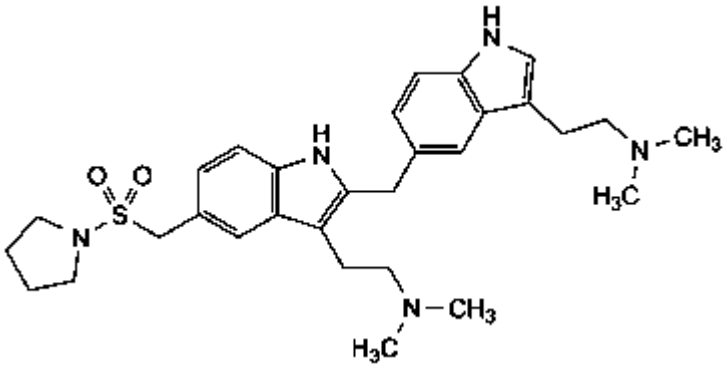
IMPURITIES

Specified impurities *A.*

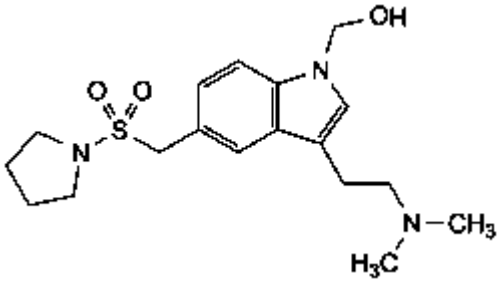
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F.*



A. *N*-methyl-2-[5-[(pyrrolidine-1-sulfonyl)methyl]-1*H*-indol-3-yl]ethan-1-amine,



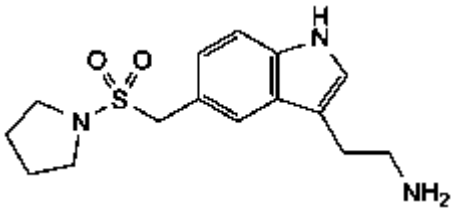
B. 2-[2-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-5-[(pyrrolidine-1-sulfonyl)methyl]-1*H*-indol-3-yl]-*N*,*N*-dimethylethan-1-amine,



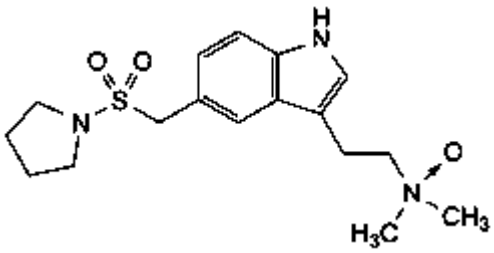
C. [3-[2-(dimethylamino)ethyl]-5-[(pyrrolidine-1-sulfonyl)methyl]-1*H*-indol-1-yl]methanol,

www.webofpharma.com

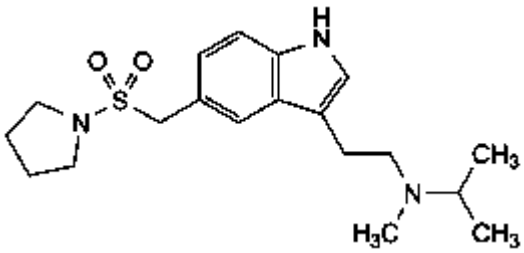
https://thuocngocanh.com/



D. 2-[5-[(pyrrolidine-1-sulfonyl)methyl]-1*H*-indol-3-yl]ethan-1-amine,



E. *N*,*N*-dimethyl-2-[5-[(pyrrolidine-1-sulfonyl)methyl]-1*H*-indol-3-yl]ethan-1-amine *N*-oxide,



F. *N*-methyl-*N*-[2-[5-[(pyrrolidine-1-sulfonyl)methyl]-1*H*-indol-3-yl]ethyl]propan-2-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alpha Tocopheryl Acetate Concentrate (Powder Form)

General Notices

(α-Tocopheryl Acetate Concentrate (Powder Form) Ph. Eur. monograph 0691)

Action and use

Used in prevention and treatment of vitamin E deficiencies.

Ph Eur

DEFINITION

Preparation obtained either by finely dispersing *all-rac-α-Tocopheryl acetate (0439)* in a suitable carrier of suitable quality (for example gelatin, acacia, carbohydrates, lactoproteins or a mixture thereof) or by adsorbing *all-rac-α-Tocopheryl acetate (0439)* on silicic acid of suitable quality.

Content

90.0 per cent to 115.0 per cent of the α-tocopheryl acetate content stated on the label, which is not less than 25 g per 100 g of concentrate.

CHARACTERS

Appearance

Almost white, yellowish or light brown, small particles.

Solubility

Practically insoluble or swells or forms a dispersion in water, depending on the formulation.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Thin-layer chromatography (*2.2.27*).

Test solution To a quantity of the preparation to be examined corresponding to 50 mg of α-tocopheryl acetate add 5 mL of *0.01 M hydrochloric acid* and treat with ultrasound at 60 °C. Add 5 mL of *anhydrous ethanol R* and 10 mL of *cyclohexane R*, shake for 1 min and centrifuge for 5 min. Use the upper layer.

Reference solution Dissolve 50 mg of *α-tocopheryl acetate CRS* in *cyclohexane R* and dilute to 10 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Plate TLC silica gel F_{254} plate R.

Mobile phase ether R, cyclohexane R (20:80 *V/V*).

Application 10 µL.

Development 3/4 of the plate.

Drying In a current of air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the assay.

Results:

— the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a);

— in the chromatogram obtained with reference solution (c) no additional principal peak is observed when compared with the chromatogram obtained with the test solution.

ASSAY

Gas chromatography (2.2.28).

Internal standard solution Dissolve 1.0 g of squalane R in cyclohexane R and dilute to 500.0 mL with the same solvent.

Test solution Weigh accurately a quantity of the preparation to be examined corresponding to about 0.100 g of α-tocopheryl acetate into a 250 mL conical flask. Add 20 mL of 1 M hydrochloric acid and sonicate at 70 °C for 20 min. Add 50 mL of anhydrous ethanol R and 50.0 mL of the internal standard solution. Mix thoroughly for 30 min using a magnetic stirrer. Allow the 2 layers to separate and use the upper layer.

Reference solution (a) Dissolve 0.100 g of α-tocopheryl acetate CRS in 50.0 mL of the internal standard solution.

Reference solution (b) Dissolve 10 mg of α-tocopherol R and 10 mg of α-tocopheryl acetate CRS in 5.0 mL of cyclohexane R.

Reference solution (c) Mix 1.0 mL of the test solution and 1.0 mL of reference solution (a).

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: methylpolysiloxane R (film thickness 0.25 µm).

Carrier gas helium for chromatography R.

www.webofpharma.com

https://thietbiuocngocanh.com/

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

— *column*: 280 °C;

— *injection port and detector*: 290 °C.

Detection Flame ionisation.

Injection 1 µL; inject directly onto the column or via a sufficiently inert, glass-lined injection port.

Run time 1.1 times the retention time of α-tocopheryl acetate.

Relative retention With reference to α-tocopheryl acetate (retention time = about 12 min): squalane = about 0.5; α-tocopherol = about 0.9.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to α-tocopherol and α-tocopheryl acetate in the chromatogram obtained with reference solution (b);

— in the chromatogram obtained with reference solution (a), the area of the peak due to α-tocopherol is not greater than 0.002 times the area of the peak due to α-tocopheryl acetate (0.2 per cent).

Calculate the percentage content of $C_{31}H_{52}O_3$ from the declared content of *α-tocopheryl acetate CRS*.

STORAGE

In an airtight, well-filled container, protected from light.

LABELLING

The label states the content of α-tocopheryl acetate, expressed in grams per 100 g of concentrate.

Ph Eur

© Crown Copyright 2022

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

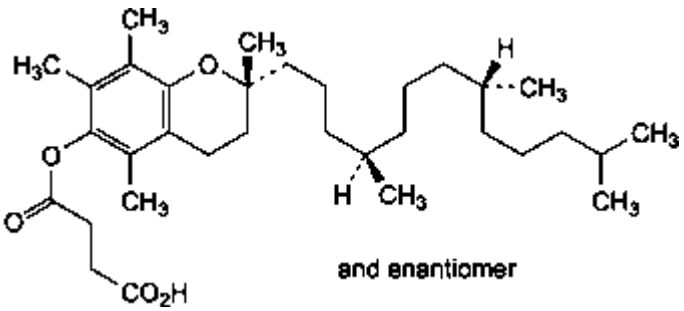
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alpha Tocopheryl Hydrogen Succinate

General Notices

(DL-α-Tocopheryl Hydrogen Succinate, Ph. Eur. monograph 1258)



$C_{33}H_{54}O_5$ 530.8

Action and use

Used in prevention and treatment of vitamin E deficiencies.

Ph Eur

DEFINITION

(2*RS*)-2,5,7,8-Tetramethyl-2-[(4*RS*,8*RS*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-yl hydrogen succinate.

Content

96.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in methylene chloride, soluble in acetone and in anhydrous ethanol.

IDENTIFICATION

First identification: B, D.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Second identification: A, C, D.

A. Absorbance (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *RRR-α-tocopheryl hydrogen succinate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 10 mg of the substance to be examined in 2 mL of *cyclohexane R*.

Test solution (b) In a ground-glass-stoppered tube, dissolve 10 mg of the substance to be examined in 2 mL of *2.5 M alcoholic sulfuric acid R*. Heat on a water-bath for 5 min. Cool and add 2 mL of *water R* and 2 mL of *cyclohexane R*. Shake for 1 min. Use the upper layer.

Reference solution (a) Dissolve 10 mg of *RRR-α-tocopheryl hydrogen succinate CRS* in 2 mL of *cyclohexane R*.

Reference solution (b) Prepare as described for test solution (b), using *RRR-α-tocopheryl hydrogen succinate CRS* instead of the substance to be examined.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *ether R*, *cyclohexane R* (0.2:20:80 *V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In a current of air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with test solution (a) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a). In the chromatograms obtained with test solution (b) and reference solution (b), there are 2 spots: the spot with the higher R_F value is due to α-tocopherol, the spot with the lower R_F value is due to DL-α-tocopheryl hydrogen succinate and corresponds to the spot obtained with reference solution (a). Depending on the degree of hydrolysis, the lower spot may be weak or even absent.

Detection B Spray with a mixture of 10 volumes of *hydrochloric acid R*, 40 volumes of a 2.5 g/L solution of *ferric chloride R* in *ethanol (96 per cent) R* and 40 volumes of a 10 g/L solution of *phenanthroline hydrochloride R* in *ethanol (96 per cent) R*.

Results B In the chromatograms obtained with test solution (b) and reference solution (b), the spot due to α-tocopherol is orange.

D. Optical rotation (see Tests).

TESTS

Optical rotation (*2.2.7*)

www.webofpharma.com

https://thuocngocanh.com/

-0.01° to + 0.01°.

Dissolve 2.50 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Absorbance (*2.2.25*)

Solution A Dissolve 0.150 g in *anhydrous ethanol R* and dilute to 100 mL with the same solvent.

Test solution (a) Dilute 10.0 mL of solution A to 100.0 mL with *anhydrous ethanol R*.

Test solution (b) Dilute 20.0 mL of solution A to 50.0 mL with *anhydrous ethanol R*.

Absorption maximum At 284 nm for test solution (a).

Absorption minimum At 254 nm for test solution (b).

Specific absorbance at the absorption maximum 35 to 38 for test solution (a).

Specific absorbance at the absorption minimum 6.0 to 8.0 for test solution (b).

Acid value (*2.5.1*)

101 to 108, determined on 1.00 g.

Free tocopherol

Maximum 1.0 per cent.

Dissolve 0.500 g in 100 mL of *0.25 M alcoholic sulfuric acid R*. Add 20 mL of *water R* and 0.1 mL of a 2.5 g/L solution of *diphenylamine R* in *sulfuric acid R*. Titrate with *0.01 M ammonium and cerium sulfate* until a blue colour is obtained that persists for at least 5 s. Carry out a blank titration.

1 mL of *0.01 M ammonium and cerium sulfate* is equivalent to 2.154 mg of free tocopherol.

Related substances

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 0.300 g of *dotriacontane R* in *hexane R* and dilute to 100.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Test solution Weigh 30.0 mg of the substance to be examined into a 20 mL vial. Add 2.0 mL of *methanol R*, 1.0 mL of *dimethoxypropane R* and 0.1 mL of *hydrochloric acid R*. Cap tightly and sonicate. Allow to stand in the dark for 1 h ± 5 min. Remove from the dark, uncap and evaporate just to dryness on a steam bath with the aid of a stream of nitrogen. Add 10.0 mL of the internal standard solution. Vortex into solution.

Reference solution Weigh 30.0 mg of *RRR-α-tocopheryl hydrogen succinate CRS* into a 20 mL vial. Add 2.0 mL of *methanol R*, 1.0 mL of *dimethoxypropane R* and 0.1 mL of *hydrochloric acid R*. Cap tightly and sonicate. Allow to stand in the dark for 1 h ± 5 min. Remove from the dark, uncap and evaporate just to dryness on a steam bath with the aid of a stream of nitrogen. Add 10.0 mL of the internal standard solution. Vortex into solution.

Column:

— *material*: fused silica;

— *size*: *l* = 15 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 3-6 mL/min.

Split ratio 1:10 to 1:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	200 → 250
	10 - 20	250
Injection port		300
Detector		330

Detection Flame ionisation.

Injection 1 µL; inject directly onto the column or via a glass-lined injection port using an automatic injection device or some other reproducible injection method.

System suitability Reference solution:

— *resolution*: minimum 12.0 between the peaks due to dotriacontane and DL-α-tocopheryl hydrogen succinate.

Interference test Dissolve 0.100 g of the substance to be examined in *hexane R* and dilute to 50.0 mL with the same solvent. Inject 1 µL of the solution and record the chromatogram. If a peak is detected with the same retention time as that of the peak due to dotriacontane,

www.webofpharma.com

https://thuvienthuocngocanh.com/

calculate the area of this peak relative to the peak area of the substance to be examined. If the relative peak area is greater than 0.5 per cent, use the corrected peak area $S'_{D(corr)}$ for the final calculation.

$$S'_{D(corr)} = S'_{D} - \frac{S_I \times S'_T}{S_{TI}}$$

S'_D = area of the peak due to dotriacontane in the chromatogram obtained with the test solution;

S_I = area of the peak with the same retention time as that of the peak due to dotriacontane in the chromatogram obtained in the interference test;

S'_T = area of the peak due to DL-α-tocopheryl hydrogen succinate in the chromatogram obtained with the test solution;

S_{TI} = area of the peak due to DL-α-tocopheryl hydrogen succinate in the chromatogram obtained in the interference test.

Measure the areas of the peaks due to *RRR-α-tocopheryl hydrogen succinate CRS* (S_T) and dotriacontane (S_D) in the chromatogram obtained with the reference solution and the areas of the peaks due to DL-α-tocopheryl hydrogen succinate (S'_T) and dotriacontane (S'_D) in the chromatogram obtained with the test solution.

Determine the response factor (RF) for DL-α-tocopheryl hydrogen succinate from the areas of the peaks due to *RRR-α-tocopheryl hydrogen succinate CRS* and dotriacontane in the chromatogram obtained with the reference solution, using the following expression:

$$\frac{S_D \times m_T}{S_T \times m_D}$$

Calculate the percentage content of DL-α-tocopheryl hydrogen succinate using the following expression:

$$\frac{100 \times S'_T \times m_D \times RF}{S'_{D(corr)} \times m}$$

S_D = area of the peak due to dotriacontane in the chromatogram obtained with the reference solution;

$S'_{D(corr)}$ = corrected area of the peak due to dotriacontane in the chromatogram obtained with the test solution;

S_T = area of the peak due to *RRR-α-tocopheryl hydrogen succinate CRS* in the chromatogram obtained with the reference solution;

S'_T = area of the peak due to DL-α-tocopheryl hydrogen succinate in the chromatogram obtained with the test solution;

m_D = mass of dotriacontane in the test solution and in the reference solution, in milligrams;

m_T = mass of *RRR-α-tocopheryl hydrogen succinate CRS* in the reference solution, in milligrams;

m = mass of the substance to be examined in the test solution, in milligrams.

STORAGE

Protected from light.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alpha Tocopheryl Succinate Tablets

General Notices

DEFINITION

Alpha Tocopheryl Succinate Tablets contain *RRR*-Alpha-Tocopheryl Hydrogen Succinate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of α-tocopherol, $C_{29}H_{50}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.134 g of α-tocopherol with three 10 mL quantities of *ether*, filter, evaporate the combined filtrates to 2 mL and then evaporate the solution to dryness under a current of nitrogen. Prepare a 0.5% w/v solution from a portion of the resulting residue in *cyclohexane*.

(2) Dissolve 10 mg of the residue obtained in the preparation of solution (1) in 2 mL of 5M *ethanolic sulfuric acid*, heat in a water bath for 1 minute, cool and add 2 mL each of *water* and *cyclohexane*. Shake for 1 minute, allow to separate and use the upper layer.

(3) 0.5% w/v of *RRR-α-tocopheryl succinate EPCRS* in *cyclohexane*.

(4) Prepare in the same manner as solution (2) but using 10 mg of *RRR-α-tocopheryl succinate EPCRS* in place of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *ether* and 80 volumes of *cyclohexane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatograms obtained with solutions (2) and (4) show two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (3).

Spray the plate with a mixture of 1 volume of *hydrochloric acid*, 4 volumes of a 0.25% w/v solution of *iron* (*III*) *chloride hexahydrate* in *ethanol* (*96%*) and 4 volumes of a 1% w/v solution of *1,10-phenanthroline hydrochloride* in *ethanol* (*96%*). In the chromatograms obtained with solutions (2) and (4) the spot of higher Rf value, due to α-tocopherol, is orange.

B. In the Assay the principal peak in the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to the methylated alpha tocopheryl succinate in the chromatogram obtained with solution (2).

TESTS

Free tocopherol

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 134 mg of α-tocopherol with three 10 mL quantities of *ether*, filter and evaporate the combined filtrates to 2 mL, evaporate the final solution to dryness under a current of nitrogen and prepare a 0.5% w/v solution from the resulting residue in *cyclohexane*.

(2) 0.005% w/v of *α-tocopherol BPCRS* in *cyclohexane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* HF_{254} as the coating substance.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *ether* and 80 volumes of *cyclohexane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the principal spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B. Dissolve 0.15 g of *dotriacontane* (internal standard) in sufficient *hexane* to produce 100 mL (solution A).

(1) Mix a quantity of the powdered tablets containing the equivalent of 134 mg of α-tocopherol with 20 mL of *methanol*, mix with the aid of ultrasound for 5 minutes and centrifuge for 15 minutes. To 4 mL of the clear supernatant liquid add 2 mL of *2,2-dimethoxypropane* and 0.2 mL of *hydrochloric acid* and allow to stand in the dark at room temperature for 1 hour. Evaporate to dryness on a water bath with the aid of a current of nitrogen and dissolve the residue in 10 mL of solution A.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dissolve 0.165 g of *RRR-α-tocopheryl succinate EPCRS* in 20 mL of *methanol*, add 2 mL of *2,2-dimethoxypropane* and 0.2 mL of *hydrochloric acid* and allow to stand in the dark at room temperature for 1 hour. Evaporate to dryness on a water bath with the aid of a current of nitrogen and dissolve the residue in 10 mL of solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a borosilicate glass column (2 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) (Chromosorb W/AW is suitable) coated with 2 to 5% of polymethylsiloxane.

(b) Use a rate of flow of carrier gas at values such that the required resolution is achieved (40 mL per minute is suitable).

(c) Set the temperature of the column such that the required resolution is achieved (a column temperature of 280° is suitable).

(d) Maintain the temperature of the injection port at 290° and the detector at 350°.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (1), the retention times of dotriacontane and methyl α-tocopheryl succinate are about 8 minutes and 20 minutes, respectively.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{50}O_2$ from the areas of the peaks due to dotriacontane and methyl α-tocopheryl succinate in the chromatograms obtained with solution (1) and solution (2) and from the declared content of $C_{29}H_{50}O_2$ in *RRR-α-tocopheryl succinate EPCRS*.

STORAGE

Alpha Tocopheryl Succinate Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of α-tocopherol.

© Crown Copyright 2022

www.webofpharma.com

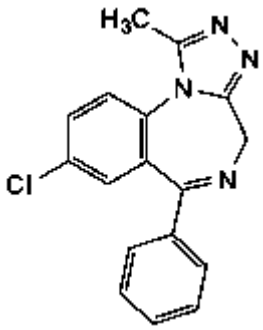
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alprazolam

General Notices

(Ph. Eur. monograph 1065)



$C_{17}H_{13}ClN_4$ 308.8 *28981-97-7*

Action and use

Benzodiazepine.

Ph Eur

DEFINITION

8-Chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: B.

Second identification: A, C.

A. Dissolve the substance to be examined in the smallest necessary quantity of *ethyl acetate R* and evaporate to dryness on a water-bath. Thoroughly mix 5.0 mg of the substance to be examined with 5.0 mg of *alprazolam CRS*. The melting point (2.2.14) of the mixture does not differ by more than 2 °C from the melting point of the substance to be examined.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *alprazolam CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethyl acetate R*, evaporate to dryness on a water-bath and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *alprazolam CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *alprazolam CRS* and 10 mg of *midazolam CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *methanol R*, *ethyl acetate R* (2:15:20:80 *V/V/V/V*).

Application 5 µL.

Development Over a path of 12 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separately spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29).

www.webofpharma.com

https://thuvienthuocngocanh.com/

Buffer solution Dissolve 7.7 g of *ammonium acetate R* in 1000 mL of *water for chromatography R* and adjust to pH 4.2 with *glacial acetic acid R*.

Test solution Dissolve 0.100 g of the substance to be examined in *dimethylformamide R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2 mg of *alprazolam CRS* and 2 mg of *triazolam CRS* in *dimethylformamide R* and dilute to 100 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with *dimethylformamide R*. Dilute 0.5 mL of this solution to 10.0 mL with *dimethylformamide R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded phenylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: buffer solution, *methanol R* (44:56 *V/V*);

— *mobile phase B*: buffer solution, *methanol R* (5:95 *V/V*);

— *temperature*: 40 °C;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	98	2
15 - 35	98 → 1	2 → 99
35 - 40	1	99

Flow rate 2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL; inject *dimethylformamide R* as a blank.

Retention time Triazolam = about 9 min; alprazolam = about 10 min.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to triazolam and alprazolam.

Limits:

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

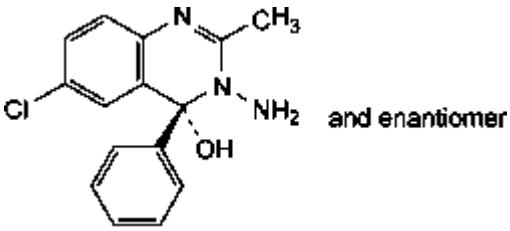
Dissolve 0.140 g in 50 mL of a mixture of 2 volumes of *acetic anhydride R* and 3 volumes of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Titrate to the 2nd point of inflexion.

1 mL of *0.1 M perchloric acid* is equivalent to 15.44 mg of $C_{17}H_{13}ClN_4$.

STORAGE

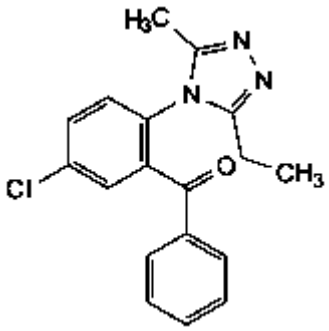
Protected from light.

IMPURITIES



and enantiomer

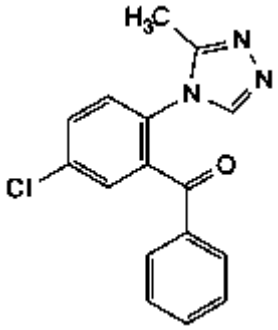
A. (4*RS*)-3-amino-6-chloro-2-methyl-4-phenyl-3,4-dihydroquinazolin-4-ol,



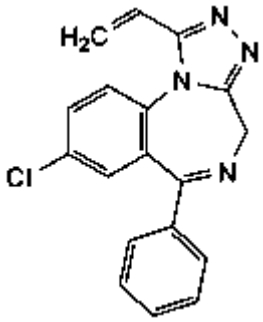
B. [5-chloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone,

www.webofpharma.com

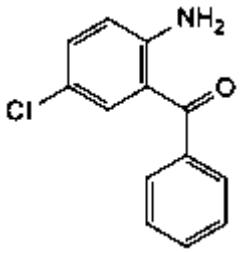
https://thuocngocanh.com/



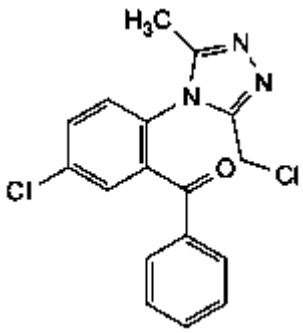
C. [5-chloro-2-[3-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone,



D. 8-chloro-1-ethenyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine,



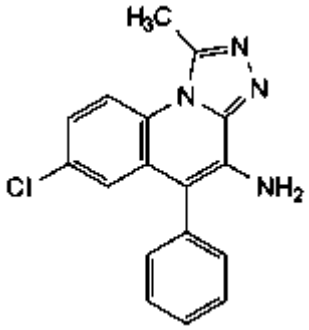
E. (2-amino-5-chlorophenyl)phenylmethanone,



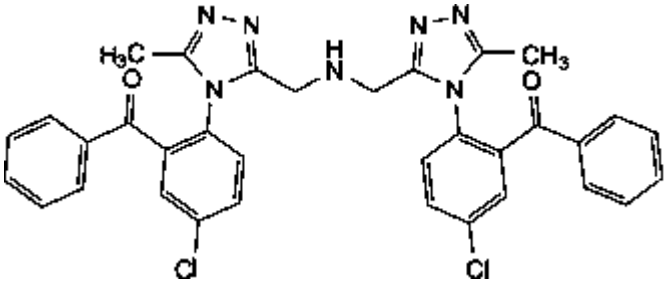
F. [5-chloro-2-[3-(chloromethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone,

www.webofpharma.com

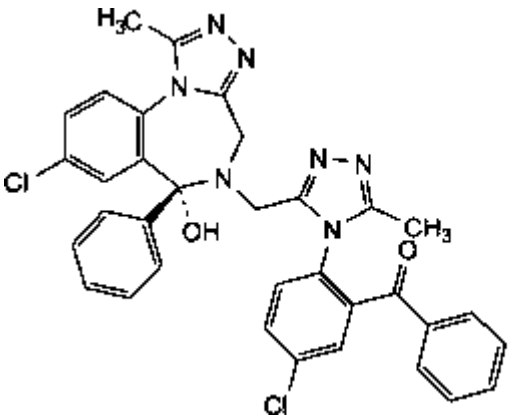
https://thuocngocanh.com/



G. 7-chloro-1-methyl-5-phenyl[1,2,4]triazolo[4,3-*a*]quinolin-4-amine,

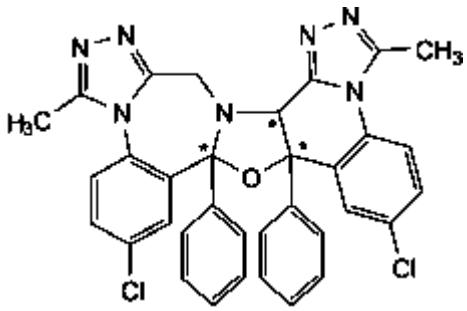


H. bis[[4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazol-3-yl]methyl]amine,



and enantiomer

I. [5-chloro-2-[3-[[(6*RS*)-8-chloro-6-hydroxy-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-5(6*H*)-yl]methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone,



J. 2,17-dichloro-6,13-dimethyl-18b,19a-diphenyl-8b,19adihydro-10*H*,18b*H*-[1,2,4]triazolo[4‴,3‴:1″,2″]quinolo[3″,4″:4′,5′]oxazolo[3′,2′-*d*]-1,2,4-triazolo[4,3-*a*][1,4]benzodiazepine.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

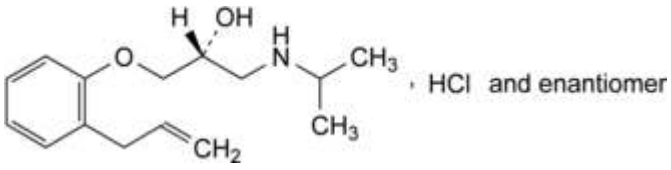
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alprenolol Hydrochloride

General Notices

(Ph. Eur. monograph 0876)



$C_{15}H_{24}ClNO_2$ 285.8 *13707-88-5*

Action and use

Beta-adrenoceptor antagonist.

Ph Eur

DEFINITION

(2*RS*)-1-[(1-Methylethyl)amino]-3-[2-(prop-2-enyl)phenoxy]propan-2-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 108 °C to 112 °C.

www.webofpharma.com

https://thuocngocanh.com/

B. Infrared absorption spectrophotometry (2.2.24).

Comparison alprenolol hydrochloride CRS.

C. Examine the chromatograms obtained in the test for impurity D.

Detection Examine in daylight, after exposure to iodine vapour for 30 min.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in carbon dioxide-free water R and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_9 (2.2.2, Method II).

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of methyl red solution R and 0.2 mL of 0.01 M hydrochloric acid; the solution is red. Add 0.4 mL of 0.01 M sodium hydroxide; the solution is yellow.

Impurity C

Maximum 0.1 per cent.

Dissolve 0.25 g in ethanol (96 per cent) R and dilute to 25 mL with the same solvent. The absorbance (2.2.25) measured at 297 nm is not greater than 0.20.

Impurity D

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.50 g of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 50 mL with methanol R.

Reference solution (a) Dissolve 10 mg of alprenolol hydrochloride CRS in methanol R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of alprenolol hydrochloride CRS and 10 mg of oxprenolol hydrochloride CRS in methanol R and dilute to 10 mL with the same solvent.

Reference solution (c) Dilute 5 mL of test solution (b) to 50 mL with methanol R.

www.webofpharma.com

https://thuocngocanh.com/

Plate *TLC silica gel G plate R*.

Mobile phase Place 2 beakers each containing 30 mL of *ammonia R* at the bottom of the tank containing a mixture of 5 volumes of *methanol R* and 95 volumes of *ethyl acetate R*.

Application 5 µL.

Development Over a path of 15 cm in a tank saturated for at least 1 h.

Drying At 100 °C for 15 min.

Detection Expose to iodine vapour for up to 6 h.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limits Test solution (a):

— *impurity D*: any spot with an R_F value greater than that of the principal spot is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.2 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 4.0 mg of *alprenolol hydrochloride CRS* and 0.8 mg of *4-isopropylphenol R* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 4.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 0.656 g of *sodium octanesulfonate R* with 150 mL of *acetonitrile R* and dilute to 500 mL with phosphate buffer pH 2.8 prepared as follows: mix 1.78 g of *phosphoric acid R* and 15.6 g of *sodium dihydrogen phosphate R* and dilute to 2000 mL with *water R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Equilibration With the mobile phase for about 1 h.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL.

Run time Twice the retention time of alprenolol.

Retention time Alprenolol = about 11 min; 4-isopropylphenol = about 18 min.

System suitability Reference solution (a):

— *resolution*: minimum 5 between the peaks due to alprenolol and 4-isopropylphenol; if necessary, adjust the concentration of sodium octanesulfonate and/or acetonitrile in the mobile phase (increase the concentration of sodium octanesulfonate to increase the retention time of alprenolol and increase the concentration of acetonitrile to decrease the retention times of both compounds).

Limits:

— *unspecified impurities*: for each impurity, not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.04 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 25 mL of a mixture of equal volumes of *anhydrous ethanol R* and *water R*. Add 10 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.58 mg of $C_{15}H_{24}ClNO_2$.

STORAGE

Protected from light.

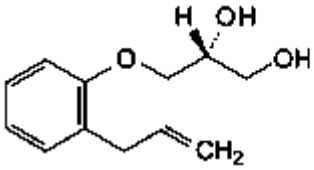
IMPURITIES

Specified impurities *C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B.*

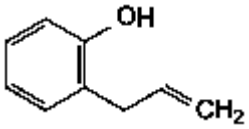
www.webofpharma.com

https://thuocngocanh.com/

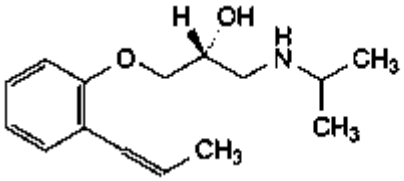


and enantiomer

A. (2*RS*)-3-[2-(prop-2-enyl)phenoxy]propan-1,2-diol,

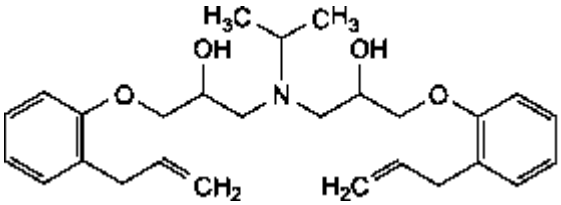


B. 2-(prop-2-enyl)phenol,



and enantiomer

C. (2*RS*)-1-[(1-methylethyl)amino]-3-[2-(prop-1-enyl)phenoxy]propan-2-ol,



D. 1,1′-[(1-methylethyl)imino]bis[3-[2-(prop-2-enyl)phenoxy]propan-2-ol].

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

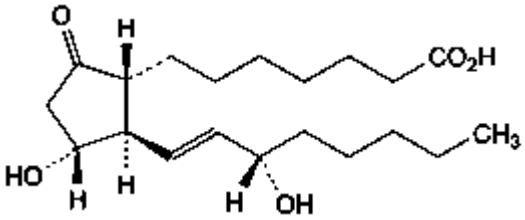
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alprostadil

General Notices

(Ph. Eur. monograph 1488)



$C_{20}H_{34}O_5$ 354.5 *745-65-3*

Action and use

Prostaglandin E_1 (PGE_1).

Ph Eur

DEFINITION

7-[(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]heptanoic acid.

Content

95.0 per cent to 102.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in acetone, slightly soluble in ethyl acetate.

IDENTIFICATION

A. Specific optical rotation (2.2.7): -70 to -60 (anhydrous substance).

Immediately before use, dissolve 50 mg in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison alprostadil CRS.

C. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions protected from light.*

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of equal volumes of acetonitrile R1 and water R and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 100 µL of the test solution to 20.0 mL with a mixture of equal volumes of acetonitrile R1 and water R.

Reference solution (b) Dissolve 1.0 mg of dinoprostone impurity C CRS (alprostadil impurity H) and 1.0 mg of the substance to be examined in a mixture of equal volumes of acetonitrile R1 and water R and dilute to 20.0 mL with the same mixture of solvents.

Reference solution (c) In order to prepare impurities A and B *in situ*, dissolve 1 mg of the substance to be examined in 100 µL of 1 M sodium hydroxide (the solution becomes brownish-red), wait for 3 min and add 100 µL of a 112 g/L solution of phosphoric acid R (yellowish-white opalescent solution); dilute to 5.0 mL with a mixture of equal volumes of acetonitrile R1 and water R.

System A

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: base-deactivated octylsilyl silica gel for chromatography R (4 µm) with a pore size of 6 nm;

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.9 g of sodium dihydrogen phosphate R in water R and dilute to 1.0 L with the same solvent; adjust to pH 2.5 with a 2.9 g/L solution of phosphoric acid R (approximately 600 mL is required); to 740 mL of the buffer solution add 260 mL of acetonitrile R1;

— *mobile phase B*: dissolve 3.9 g of sodium dihydrogen phosphate R in water R and dilute to 1.0 L with the same solvent; adjust to pH 2.5 with a 2.9 g/L solution of phosphoric acid R (approximately 600 mL is required); to 200 mL of the buffer solution add 800 mL of acetonitrile R1;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 75	100	0
75 - 76	100 → 0	0 → 100
76 - 86	0	100
86 - 87	0 → 100	100 → 0
87 - 102	100	0

Flow rate 1 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 20 µL.

Retention time Alprostadil = about 63 min.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity H and alprostadil in the chromatogram obtained with reference solution (b).

System B

Use the same conditions as for system A with the following mobile phase and elution programme:

— *mobile phase A*: dissolve 3.9 g of *sodium dihydrogen phosphate R* in *water R* and dilute to 1.0 L with the same solvent; adjust to pH 2.5 with a 2.9 g/L solution of *phosphoric acid R* (approximately 600 mL is required); to 600 mL of the buffer solution add 400 mL of *acetonitrile R1*;

— *mobile phase B*: use mobile phase B as described under system A;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	100	0
50 - 51	100 → 0	0 → 100
51 - 61	0	100
61 - 62	0 → 100	100 → 0
62 - 72	100	0

Relative retention With reference to alprostadil (retention time = about 7 min): impurity A = about 2.4; impurity B = about 2.6.

www.webofpharma.com

https://thuocngocanh.com/

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity A and impurity B in the chromatogram obtained with reference solution (c).

Carry out the test according to system A and B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the impurities listed in Table 1488.-1 by the corresponding correction factor;

Table 1488.-1.

Impurity	Relative retention (system A)	Relative retention (system B)	Correction factor
impurity G	0.80	-	0.7
impurity F	0.88	-	0.8
impurity D	0.90	-	1.0
impurity H	0.96	-	0.7
impurity E	1.10	-	0.7
impurity C	-	1.36	1.9
impurity K	-	1.85	0.06
impurity A	-	2.32	0.7
impurity B	-	2.45	1.5
impurity I	-	4.00	1.0
impurity J	-	5.89	1.0

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *any other impurity*: not more than 1.8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.9 per cent), and not more than 1 such peak has an area greater than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Evaluate impurities appearing at relative retentions less than 1.2 by system A and impurities appearing at relative retentions greater than 1.2 by system B;

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 50 mg.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances, system A. *Prepare the solutions protected from light.*

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of equal volumes of *acetonitrile R1* and *water R* and dilute to 25.0 mL with the same mixture of solvents. Dilute 3.0 mL of the solution to 20.0 mL with a mixture of equal volumes of *acetonitrile R1* and *water R*.

Reference solution Dissolve 5.0 mg of *alprostadil CRS* in a mixture of equal volumes of *acetonitrile R1* and *water R* and dilute to 25.0 mL with the same mixture of solvents. Dilute 6.0 mL of the solution to 20.0 mL with a mixture of equal volumes of *acetonitrile R1* and *water R*.

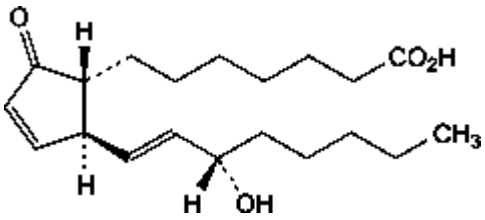
Injection 20 µL.

Calculate the percentage content of $C_{20}H_{34}O_5$ taking into account the assigned content of *alprostadil CRS*.

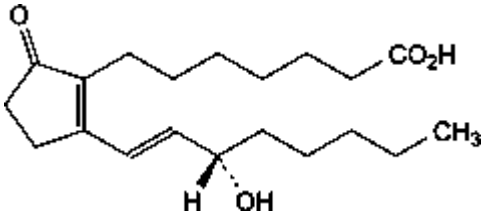
STORAGE

At a temperature of 2 °C to 8 °C.

IMPURITIES



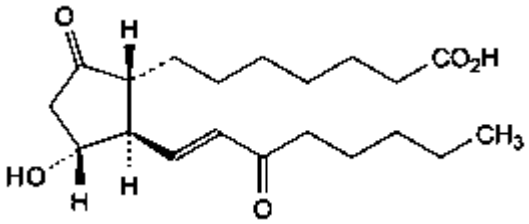
A. 7-[(1*R*,2*S*)-2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopent-3-enyl]heptanoic acid (prostaglandin A_1),



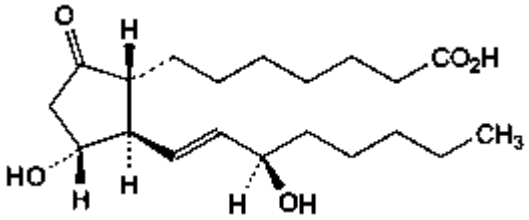
B. 7-[2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopent-1-enyl]heptanoic acid (prostaglandin B_1),

www.webofpharma.com

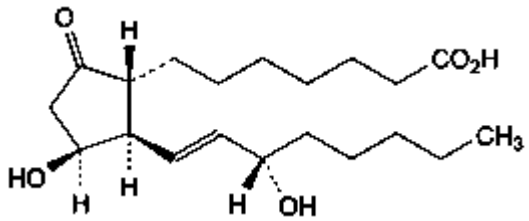
https://thuocngocanh.com/



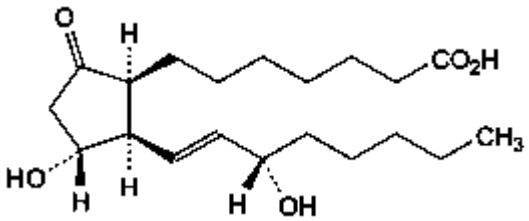
C. 7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(1*E*)-3-oxooct-1-enyl]-5-oxocyclopentyl]heptanoic acid (15-oxoprostaglandin E_1),



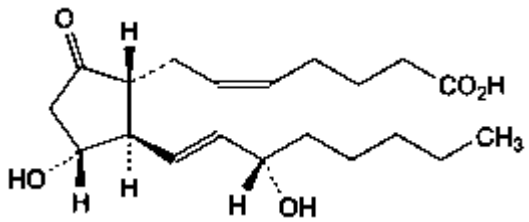
D. 7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(1*E*,3*R*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]heptanoic acid (15-epiprostaglandin E_1),



E. 7-[(1*R*,2*R*,3*S*)-3-hydroxy-2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]heptanoic acid (11-epiprostaglandin E_1),



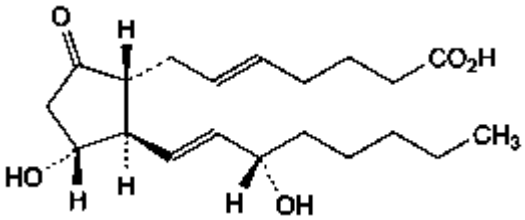
F. 7-[(1*S*,2*R*,3*R*)-3-hydroxy-2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]heptanoic acid (8-epiprostaglandin E_1),



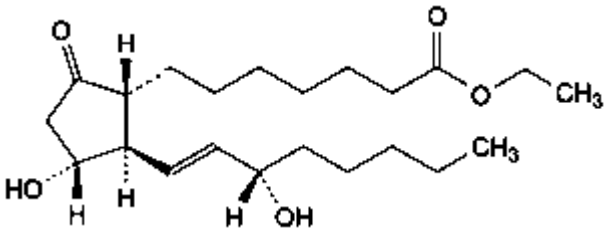
G. (5*Z*)-7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid (dinoprostone),

www.webofpharma.com

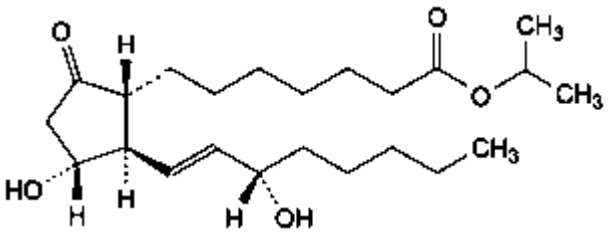
https://thuocngocanh.com/



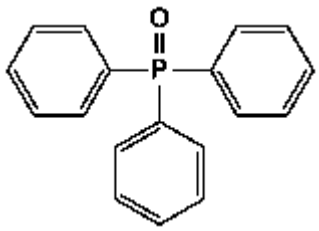
H. (5*E*)-7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid ((5*E*)-prostaglandin E_2),



I. ethyl 7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]heptanoate (prostaglandin E_1, ethyl ester),



J. 1-methylethyl 7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(1*E*,3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]heptanoate (prostaglandin E_1, isopropyl ester),



K. triphenylphosphine oxide.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Alteplase for Injection

General Notices

(Ph. Eur. monograph 1170)

Action and use

Tissue-type plasminogen activator; fibrinolytic.

Ph Eur

DEFINITION

Alteplase for injection is a sterile, freeze-dried preparation of alteplase, a tissue plasminogen activator produced by recombinant DNA technology. It has a potency of not less than 500 000 IU per milligram of protein.

Tissue plasminogen activator binds to fibrin clots and activates plasminogen, leading to the generation of plasmin and to the degradation of fibrin clots or blood coagulates.

Alteplase consists of 527 amino acids with a calculated relative molecular mass of 59 050 without consideration of the carbohydrate moieties attached at positions Asn 117, Asn 184 and Asn 448. The total relative molecular mass is approximately 65 000. Alteplase is

www.webofpharma.com

https://thuvienthuocngocanh.com/

cleaved by plasmin between amino-acids 275 and 276 into a two-chain form (A chain and B chain) that are connected by a disulfide bridge between Cys 264 and Cys 395. The single-chain form and the two-chain form show comparable fibrinolytic activity *in vitro*.

PRODUCTION

Alteplase is produced by recombinant DNA synthesis in cell culture; the fermentation takes place in serum-free medium.

The purification process is designed to remove efficiently potential impurities, such as antibiotics, DNA and protein contaminants derived both from the host cell and from the production medium, and potential viral contaminants.

If alteplase is stored in bulk form, stability (maintenance of potency) in the intended storage conditions must be demonstrated.

The production, purification and product consistency are checked by a number of analytical methods described below, carried out routinely as in-process controls.

Protein content

The protein concentration of alteplase solutions is determined by measuring the absorbance (2.2.25) of the protein solution at 280 nm and at 320 nm, using formulation buffer as the compensation liquid. If dilution of alteplase samples is necessary, the samples are diluted in formulation buffer. For the calculation of the alteplase concentration, the absorbance value (A_{280} - A_{320}) is divided by the specific absorption coefficient for alteplase of 1.9.

Potency

The potency of alteplase is determined in an *in vitro* clot-lysis assay as described under Assay. The specific activity of bulk alteplase is approximately 580 000 IU per milligram of alteplase.

N-terminal sequence

N-terminal sequencing is applied to determine the correct *N*-terminal sequence and to determine semiquantitatively additional cleavage sites in the alteplase molecule, for example at position AA 275-276 or at position AA 27-28. The *N*-terminal sequence must conform with the sequence of human tissue plasminogen activator.

Isoelectric focusing

The consistency in the microheterogeneity of glycosylation of the alteplase molecule can be demonstrated by isoelectric focusing (IEF). A complex banding pattern with 10 major and several minor bands in the pH range 6.5-8.5 is observed. Denaturing conditions are applied to achieve a good separation of differently charged variants of alteplase. The broad charge distribution observed is due to a population of molecules, which differ in the fine structure of biantenary and triantenary complex-type carbohydrate residues, with different degrees of substitution with sialic acids. The banding pattern of alteplase test samples must be consistent with the pattern of alteplase reference standard.

Single-chain alteplase content

The alteplase produced by CHO (Chinese hamster ovary) cells in serum-free medium is predominantly single-chain alteplase. The single-chain form can be separated from the two-chain form by gel-permeation liquid chromatography under reducing conditions as described

www.webofpharma.com

https://thuocngocanh.com/

under Single-chain content (see Tests). The single-chain alteplase content in bulk samples must be higher than 60 per cent.

Tryptic-peptide mapping

The primary structure of the alteplase molecule is verified by tryptic-peptide mapping as described under Identification B. The reduced and carboxymethylated molecule is cleaved by trypsin into about 50 peptides, which are separated by reverse-phase liquid chromatography. A characteristic chromatogram (fingerprint) is obtained. The identity of the tryptic-peptide map of a given alteplase sample with the profile of a well-characterised reference standard is an indirect confirmation of the amino-acid sequence, because even single amino-acid exchanges in individual peptides can be detected by this sensitive technique. In addition, complex peaks of the glycopeptides can be isolated from the tryptic-peptide map and separated in a second dimension, either by reverse-phase liquid chromatography under modified conditions or by capillary electrophoresis. By this two-dimensional separation of glycopeptide variants, lot-to-lot consistency of the microheterogeneity of glycosylation can be demonstrated.

The tryptic-peptide map of alteplase samples must be consistent with the tryptic-peptide map of alteplase reference standard.

Monomer content

The monomer content of alteplase is measured by gel-permeation liquid chromatography under non-reduced conditions as described under Monomer content (see Tests). The monomer content of alteplase bulk samples must be higher than 95 per cent.

Type I/Type II alteplase content

CHO cells produce 2 glycosylation variants of alteplase. Type I alteplase contains 1 polymannose-type glycosylation at position Asn 117 and 2 complex-type glycosylation sites at positions Asn 184 and Asn 448. Type II alteplase is only glycosylated at positions Asn 117 and Asn 448.

The ratio of Type I/Type II alteplase is constant in the range of 45 to 65 per cent of Type I and 35 to 55 per cent of Type II. The content of alteplase Type I and Type II can be determined by a densitometric scan of SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) gel. Plasmin-treated samples of alteplase, which are reduced and carboxymethylated before loading on the gel, are separated into 3 bands: Type I alteplase A-chain (AA 1-275), Type II alteplase A-chain (AA 1-275) and alteplase B-chain (AA 276-527). The ratio of Type I/Type II alteplase is determined from a calibration curve, which is obtained by a densitometric scan of defined mixtures of purified Type I alteplase and Type II alteplase standards.

SDS-PAGE

SDS-PAGE (silver staining) is used to demonstrate purity of the alteplase bulk material and the integrity of the alteplase molecule. For alteplase bulk samples, no additional protein bands compared to reference standard or degradation products must occur in SDS-PAGE gels at a loading amount of 2.5 µg alteplase protein per lane and a limit of detection of 5 ng per protein (BSA) band.

Bacterial endotoxins (*2.6.14*)

Less than 1 IU per milligram of alteplase.

Sialic acids

www.webofpharma.com

https://thuocngocanh.com/

Proceed using a suitable validated method developed according to general chapter 2.2.59. *Glycan analysis of glycoproteins*. The sialic acids content for the test samples must be in the range of 70 to 130 per cent compared to alteplase reference standard, which contains about 3 moles of sialic acids per mole of alteplase.

Neutral sugars

Dilute alteplase samples and the reference standard in the assay buffer, containing 34.8 g/L of *arginine R*, 0.1 g/L of *polysorbate 80 R* and adjusted to pH 7.4 with *phosphoric acid R*, to a protein concentration of 50 µg/mL. Prepare the following concentrations of mannose in the same assay buffer for a calibration curve: 20, 30, 40, 50 and 60 µg/mL. Pipette 2 mL of alteplase samples and reference standard, as well as 2 mL of each mannose concentration in duplicate in reagent tubes. Add 50 µL of *phenol R*, followed by 5 mL of *sulfuric acid R*, in each reagent tube. Incubate the mixture for 30 min at room temperature. Measure the absorbance at 492 nm for each tube. Read the content of neutral sugars from the mannose calibration curve. The neutral sugar content is expressed in moles of neutral sugar per mole of alteplase, taking into account the dilution factor for alteplase samples and reference standard and using a relative molecular mass of 180.2 for mannose and a relative molecular mass of 59 050 for the alteplase protein moiety. The neutral sugar content of the alteplase samples must be in the range of 70 to 130 per cent compared to alteplase reference standard, which contains about 12 moles of neutral sugar per mole of alteplase.

CHARACTERS

White or slightly yellow powder or friable mass.

Reconstitute the preparation as stated on the label immediately before carrying out the Identification, Tests (except those for solubility and water) and Assay.

IDENTIFICATION

A. The assay serves also to identify the preparation.

B. Tryptic-peptide mapping. Examine by liquid chromatography (2.2.29).

Test solution Dilute the preparation to be examined with *water R* to obtain a solution containing about 1 mg of alteplase per millilitre. Dialyse about 2.5 mL of the solution for at least 12 h into a solution containing 480 g/L of *urea R*, 44 g/L of *tris(hydroxymethyl)aminomethane R* and 1.5 g/L of *sodium edetate R* and adjusted to pH 8.6, using a membrane with a cut-off point corresponding to a relative molecular mass of 10 000 for globular proteins. Measure the volume of the solution, transfer it to a clean test-tube and add per millilitre 10 µL of a 156 g/L solution of *dithiothreitol R*. Allow to stand for 4 h, cool in iced water and add per millilitre of solution 25 µL of a freshly prepared 190 g/L solution of *iodoacetic acid R*. Allow to stand in the dark for 30 min. Add per millilitre 50 µL of dithiothreitol solution to stop the reaction. Dialyse for 24 h against an 8 g/L solution of *ammonium hydrogen carbonate R*. Add 1 part of *trypsin for peptide mapping R* to 100 parts of the protein and allow to stand for 6 h to 8 h. Repeat the addition of trypsin and allow to stand for a total of 24 h.

Reference solution Prepare as for the test solution using a suitable reference standard instead of the preparation to be examined.

The chromatographic procedure may be carried out using:

— a column 0.1 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm to 10 µm);

www.webofpharma.com

https://thuvienthuocngocanh.com/

Mobile phase A 8 g/L solution of *sodium dihydrogen phosphate R*, adjusted to pH 2.85 with *phosphoric acid R*, filtered and degassed;

Mobile phase B 75 per cent *V/V* solution of *acetonitrile R* in mobile phase A;

— as detector a spectrophotometer set at 210 nm.

Equilibrate the system with mobile phase A at a flow rate of 1 mL/min. After injection of the solution, increase the proportion of mobile phase B at a rate of 0.44 per cent per minute until the ratio of mobile phase A to mobile phase B is 60:40, then increase the proportion of mobile phase B at a rate of 1.33 per cent per minute until the ratio of mobile phase A to mobile phase B is 20:80 and then continue elution with this mixture for a further 10 min. Record the chromatogram for the reference solution: the test is not valid unless the resolution of peaks 6 (peptides 268-275) and 7 (peptides 1-7) is at least 1.5; w_{h1} and w_{h2} are not more than 0.4 min. Inject about 100 µL of the test solution and record the chromatogram. Verify the identity of the peaks by comparison with the chromatograms of the reference solution. There should not be any additional significant peaks or shoulders, a significant peak or shoulder being defined as one with an area response equal to or greater than 5 per cent of peak 19 (peptides 278-296); no significant peak is missing. A type chromatogram for identification of the peaks cited is shown in Figure 1170.-1.

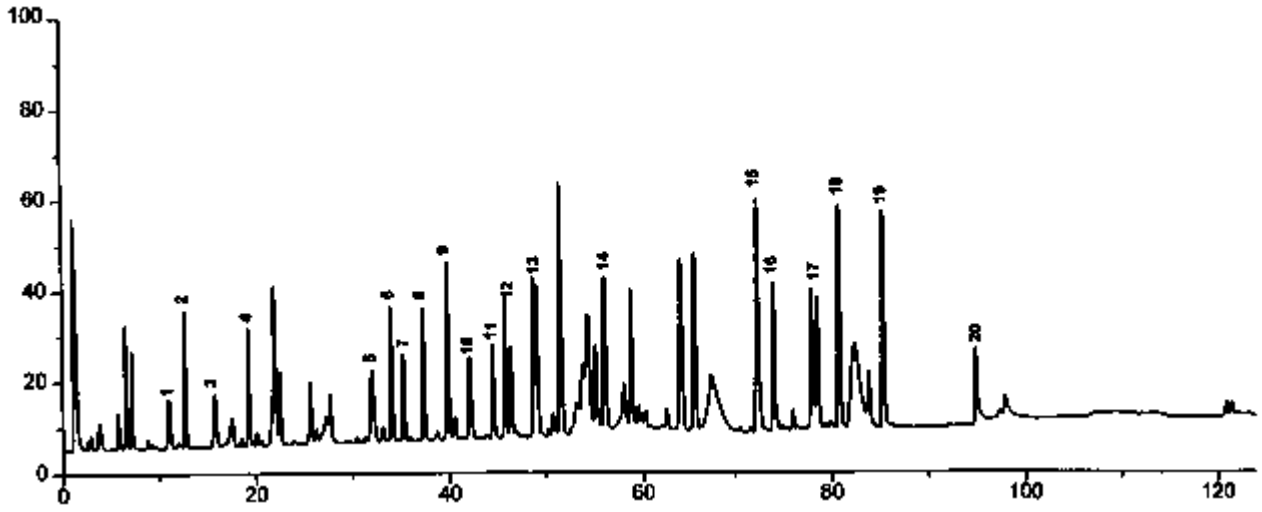


Figure 1170.-1. – *Chromatogram for tryptic-peptide mapping of alteplase*

TESTS

Appearance of solution

The reconstituted preparation is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

7.1 to 7.5.

Solubility

Add the volume of the liquid stated on the label. The preparation dissolves completely within 2 min at 20 °C to 25 °C.

www.webofpharma.com

https://thuocngocanh.com/

Protein content

Prepare a solution of the substance to be examined with an accurately known concentration of about 1 g/L. Using a 34.8 g/L solution of *arginine R* adjusted to pH 7.3 with *phosphoric acid R*, dilute an accurately measured volume of the solution of the substance to be examined so that the absorbance measured at the maximum at about 280 nm is 0.5 to 1.0 (*test solution*). Measure the absorbance (2.2.25) of the solution at the maximum at about 280 nm and at 320 nm using the arginine solution as the compensation liquid. Calculate the protein content in the portion of alteplase taken from the following expression:

$$\frac{V\left(A_{280}-A_{320}\right)}{1.9}$$

in which V is the volume of the test solution, A_{280} is the absorbance at the maximum at about 280 nm and A_{320} is the absorbance at 320 nm.

Single-chain content

Examine by liquid chromatography (2.2.29).

Test solution Dissolve the preparation to be examined in *water R* to obtain a solution containing about 1 mg of alteplase per millilitre. Place about 1 mL of the solution in a tube, add 3 mL of a 3 g/L solution of *dithiothreitol R* in the mobile phase, place a cap on the tube and heat at about 80 °C for 3 min to 5 min.

The chromatographic procedure may be carried out using:

— a column 0.6 m long and 7.5 mm in internal diameter packed with silica-based, rigid, hydrophilic gel with spherical particles 10 µm to 13 µm in diameter, suitable for size-exclusion chromatography;

— as mobile phase at a flow rate of 0.5 mL/min a solution containing 30 g/L of *sodium dihydrogen phosphate R* and 1 g/L of *sodium dodecyl sulfate R*, adjusted to pH 6.8 with *dilute sodium hydroxide solution R*;

— as detector a spectrophotometer set at 214 nm.

Inject about 50 µL of the test solution and record the chromatogram. The chromatogram shows 2 major peaks corresponding to single-chain and two-chain alteplase. Calculate the relative amount of single-chain alteplase from the peak area values.

The test is not valid unless: the number of theoretical plates calculated on the basis of the single-chain alteplase peak is at least 1000. The content of single-chain alteplase is not less than 60 per cent of the total amount of alteplase-related substances found.

Monomer content

Examine by liquid chromatography (2.2.29).

Test solution Reconstitute the preparation to be examined to obtain a solution containing about 1 mg per millilitre.

The chromatographic procedure may be carried out using:

— a column 0.6 m long and 7.5 mm in internal diameter packed with silica-based rigid, hydrophilic gel with spherical particles 10 µm to 13 µm in diameter, suitable for size-exclusion chromatography;

www.webofpharma.com

https://thuocngocanh.com/

— as mobile phase at a flow rate of 0.5 mL/min a solution containing 30 g/L of *sodium dihydrogen phosphate R* and 1 g/L of *sodium dodecyl sulfate R*, adjusted to pH 6.8 with *dilute sodium hydroxide solution R*;

— as detector a spectrophotometer set at 214 nm.

Inject the test solution and record the chromatogram. The test is not valid unless the number of theoretical plates calculated for the alteplase monomer peak is at least 1000. Measure the response for all peaks, i.e. peaks corresponding to alteplase species of different molecular masses. Calculate the relative content of monomer from the area values of these peaks. The monomer content for alteplase must be at least 95 per cent.

Water (*2.5.12*)

Not more than 4.0 per cent, determined by the semi-micro determination of water.

Bacterial endotoxins (*2.6.14*)

Less than 1 IU per milligram of protein.

Sterility (*2.6.1*)

It complies with the test for sterility.

ASSAY

The potency of alteplase is determined by comparing its ability to activate plasminogen to form plasmin with the same capacity of a reference preparation calibrated in International Units. The formation of plasmin is measured by the determination of the lysis time of a fibrin clot in given conditions.

The International Unit is the activity of a stated quantity of the International Standard of alteplase. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Solvent buffer A solution containing 1.38 g/L of *sodium dihydrogen phosphate monohydrate R*, 7.10 g/L of *anhydrous disodium hydrogen phosphate R*, 0.20 g/L of *sodium azide R* and 0.10 g/L of *polysorbate 80 R*.

Human thrombin solution A solution of *human thrombin R* containing 33 IU/mL in solvent buffer.

Human fibrinogen solution A 2 g/L solution of *fibrinogen R* in solvent buffer.

Human plasminogen solution A 1 g/L solution of *human plasminogen R* in solvent buffer.

Test solutions Using a solution of the substance to be examined containing 1 g/L, prepare serial dilutions using solvent buffer, for example 1:5000, 1:10 000, 1:20 000.

Reference solutions Using a solution of a suitable reference standard having an accurately known concentration of about 1 g/L (580 000 IU of alteplase per millilitre), prepare 5 serial dilutions using *water R* to obtain reference solutions having known concentrations in the range 9.0 IU/mL to 145 IU/mL.

www.webofpharma.com

https://thuocngocanh.com/

To each of a set of labelled glass test-tubes, add 0.5 mL of human thrombin solution. Allocate each test and reference solution to a separate tube and add to each tube 0.5 mL of the solution allocated to it. To each of a second set of labelled glass tubes, add 20 µL of human plasminogen solution, and 1 mL of human fibrinogen solution, mix and store on ice. Beginning with the reference/thrombin mixture containing the lowest number of International Units per millilitre, record the time and separately add 200 µL of each of the thrombin mixtures to the test tubes containing the plasminogen-fibrinogen mixture. Using a vortex mixer, intermittently mix the contents of each tube for a total of 15 s and carefully place in a rack in a circulating water-bath at 37 °C. A visibly turbid clot forms within 30 s and bubbles subsequently form within the clot. Record the clot-lysis time as the time between the first addition of alteplase solution and the moment when the last bubble rises to the surface. Using a least-squares fit, determine the equation of the line using the logarithms of the concentrations of the reference preparation in International Units per millilitre versus the logarithms of the values of their clot-lysis times in seconds, according to the following equation:

$$\log_{10} t = a + b\left(\log_{10} U_s\right)$$

in which t is the clot-lysis time, U_S the activity in International Units per millilitre of the reference preparation, b is the slope and a the y-intercept of the line. The test is not valid unless the correlation coefficient is -0.9900 to -1.0000. From the line equation and the clot-lysis time for the test solution, calculate the logarithm of the activity U_A from the following equation:

$$\log_{10} U_A = \frac{\left[\left(\log_{10} t\right) - a\right]}{b}$$

Calculate the alteplase activity in International Units per millilitre from the following expression:

$$D \times U_A$$

in which D is the dilution factor for the test solution. Calculate the specific activity in the portion of the substance to be examined from the following expression:

$$\frac{U_A}{P}$$

in which P is the concentration of protein obtained in the test for protein content.

The estimated potency is not less than 90 per cent and not more than 110 per cent of the stated potency.

STORAGE

Store in a colourless, glass container, under vacuum or under an inert gas, protected from light, at a temperature of 2 °C to 30 °C.

LABELLING

The label states:

— the number of International Units per container;

— the amount of protein per container;

— the name and volume of the liquid to be used for reconstitution.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

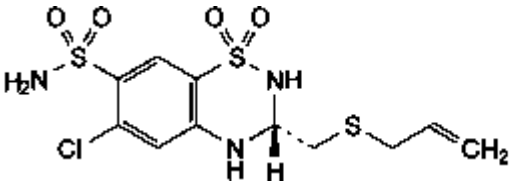
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Altizide

General Notices

(Ph. Eur. monograph 2185)



and enantiomer

$C_{11}H_{14}ClN_3O_4S_3$ 383.9 *5588-16-9*

Action and use

Thiazide diuretic.

Ph Eur

DEFINITION

(3*RS*)-6-Chloro-3-[(prop-2-enylsulfanyl)methyl]-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in methanol, practically insoluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *altizide CRS*.

www.webofpharma.com

https://thuocngocanh.com/

If the spectra obtained show differences, dissolve 50 mg of the substance to be examined and 50 mg of the reference substance separately in 2 mL of *acetone R* and evaporate the solvent. Precipitate by adding 1 mL of *methylene chloride R*. Evaporate to dryness and record new spectra using the residues.

TESTS

Impurity B

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.200 g of the substance to be examined in *acetone R* and dilute to 2.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *altizide impurity B CRS* in *acetone R* and dilute to 25.0 mL with the same solvent.

Reference solution (b) To 1.0 mL of reference solution (a) add 1.0 mL of the test solution.

Reference solution (c) Dilute 5.0 mL of reference solution (a) to 10.0 mL with *acetone R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *acetone R*, *methylene chloride R* (25:75 *V/V*).

Application 10 µL of the test solution and reference solutions (b) and (c).

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a mixture of equal volumes of a 10 g/L solution of *potassium permanganate R* and a 50 g/L solution of *sodium carbonate R*, prepared immediately before use. Allow to stand for 30 min and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limit Any spot due to impurity B is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.2 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use, except reference solution (b).*

Test solution Dissolve 50 mg of the substance to be examined in 5 mL of *acetonitrile R* and dilute to 25 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) In order to produce impurity A *in situ*, dissolve 50 mg of the substance to be examined in 5 mL of *acetonitrile R* and dilute to 25 mL with *water R*. Allow to stand for 30 min.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Dissolve 4 mg of *furosemide CRS* in 2 mL of *acetonitrile R*, add 2 mL of the test solution and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, *water for chromatography R* previously adjusted to pH 2.0 with *perchloric acid R* (25:75 *V/V*).

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 5 µL.

Run time Twice the retention time of altizide.

Relative retention With reference to altizide (retention time = about 25 min): impurity A = about 0.15; furosemide = about 1.05.

System suitability Reference solution (c):

— *resolution*: minimum 1.0 between the peaks due to altizide and furosemide.

Limits:

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 50.0 mg.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances, with the following modifications.

www.webofpharma.com

https://thuocngocanh.com/

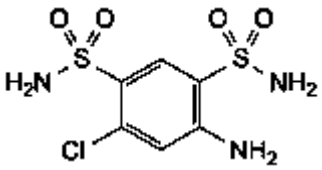
Test solution Dissolve 25.0 mg of the substance to be examined in 2 mL of *acetonitrile R* and dilute to 25.0 mL with the mobile phase.

Reference solution Dissolve 25.0 mg of *altizide CRS* in 2 mL of *acetonitrile R* and dilute to 25.0 mL with the mobile phase.

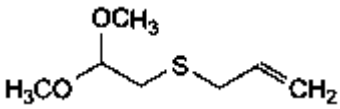
Calculate the percentage content of $C_{11}H_{14}ClN_3O_4S_3$ from the declared content of *altizide CRS*.

IMPURITIES

Specified impurities *A, B.*



A. 4-amino-6-chlorobenzene-1,3-disulfonamide,



B. 3-[(2,2-dimethoxyethyl)sulfanyl]prop-1-ene.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alum

General Notices

Potash Alum

Aluminium Potassium Sulphate

Aluminium Potassium Sulfate

(Ph. Eur. monograph 0006)

$AlK(SO_4)_2,12H_2O$ 474.4 *7784-24-9*

Action and use

Astringent.

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent of $AlK(SO_4)_2,12H_2O$.

CHARACTERS

Appearance

Granular powder or colourless, transparent, crystalline masses.

Solubility

Freely soluble in water, very soluble in boiling water, soluble in glycerol, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives the reactions of sulfates (*2.3.1*).

B. Solution S gives the reaction of aluminium (*2.3.1*).

C. Shake 10 mL of solution S with 0.5 g of *sodium hydrogen carbonate R* and filter. The filtrate gives reaction (a) of potassium (*2.3.1*).

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 2.5 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

3.0 to 3.5.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Ammonium (*2.4.1*)

Maximum 0.2 per cent.

To 1 mL of solution S add 4 mL of *water R*. Dilute 0.5 mL of this solution to 14 mL with *water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 2 mL of solution S to 10 mL with *water R*. Use in this test 0.3 mL of *thioglycollic acid R*.

ASSAY

Dissolve 0.900 g in 20 mL of *water R* and carry out the complexometric titration of aluminium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 47.44 mg of $AlK(SO_4)_2,12H_2O$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Acetate Ear Drops

General Notices

DEFINITION

Aluminium Sulfate	225 g
Calcium Carbonate	100 g
Tartaric Acid	45 g
Acetic Acid (33 per cent)	250 mL
Purified Water	750 mL

Extemporaneous preparation

The following directions apply.

Dissolve the Aluminium Sulfate in 600 mL of the Purified Water, add the Acetic Acid and then the Calcium Carbonate mixed with the remainder of the Purified Water and allow to stand for not less than 24 hours in a cool place, stirring occasionally. Filter, add the Tartaric Acid to the filtrate and mix.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of aluminium, Al

1.7 to 1.9% w/v.

CHARACTERISTICS

A clear liquid.

Weight per mL

1.06 to 1.08 g, Appendix V G.

ASSAY

Dilute 10 mL to 100 mL with *water*. To 10 mL of the resulting solution add 40 mL of 0.05M *disodium edetate VS*, 90 mL of *water* and 0.15 mL of *methyl red solution*. Neutralise by the drop wise addition of 1M *sodium hydroxide* and warm on a water bath for 30 minutes. Cool, add 1 mL of 2M *nitric acid* and 5 g of *hexamine* and titrate with 0.05M *lead nitrate VS* using 0.5 mL of *xylenol orange solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 1.349 mg of Al.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

Aluminium Acetate Ear Drops should be kept in a well-filled container.

When aluminium acetate solution or Burow's Solution is prescribed or demanded a solution complying with the requirements of this monograph shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Chloride Hexahydrate

General Notices

(Ph. Eur. monograph 0971)

$AlCl_3,6H_2O$ 241.4 *7784-13-6*

Action and use

Astringent.

Preparation

Aluminium Chloride Solution

Ph Eur

DEFINITION

Content

95.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or slightly yellow, crystalline powder or colourless crystals, deliquescent.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), soluble in glycerol.

IDENTIFICATION

A. Dilute 0.1 mL of solution S2 (see Tests) to 2 mL with *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

B. Dilute 0.3 mL of solution S2 to 2 mL with *water R*. The solution gives the reaction of aluminium (*2.3.1*).

TESTS

Solution S1

Dissolve 10.0 g in *distilled water R* and dilute to 100 mL with the same solvent.

Solution S2

www.webofpharma.com

https://thuocngocanh.com/

Dilute 50 mL of solution S1 to 100 mL with *water R*.

Appearance of solution

Solution S2 is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S1.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S1.

Alkali and alkaline-earth metals

Maximum 0.5 per cent.

To 20 mL of solution S2 add 100 mL of *water R* and heat to boiling. To the hot solution add 0.2 mL of *methyl red solution R*. Add *dilute ammonia R1* until the colour of the indicator changes to yellow and dilute to 150 mL with *water R*. Heat to boiling and filter. Evaporate 75 mL of the filtrate to dryness on a water-bath and ignite to constant mass. The residue weighs a maximum of 2.5 mg.

Water (*2.5.12*)

42.0 per cent to 48.0 per cent, determined on 50.0 mg.

ASSAY

Dissolve 0.500 g in 25.0 mL of *water R*. Carry out the complexometric titration of aluminium (*2.5.11*). Titrate with *0.1 M zinc sulfate* until the colour of the indicator changes from greyish-green to pink. Carry out a blank titration.

1 mL of *0.1 M sodium edetate* is equivalent to 24.14 mg of $AlCl_3,6H_2O$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thietbiuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Chloride Solution

General Notices

Aluminium Chloride Cutaneous Solution

DEFINITION

Aluminium Chloride Solution is a *cutaneous solution*. It contains Aluminium Chloride Hexahydrate in a suitable ethanolic vehicle.

PRODUCTION

In making Aluminium Chloride Solution, Industrial Methylated Spirits may be used provided that the law and the statutory regulations governing the use of Industrial Methylated Spirits are observed.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of aluminium chloride hexahydrate, $AlCl_3,6H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dilute the solution with *water* to produce a solution containing 2% w/v of Aluminium Chloride Hexahydrate. The solution yields reaction A characteristic of *aluminium salts* and reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Iron

Dilute the solution being examined with *water* to produce a solution containing 10.0% w/v of Aluminium Chloride Hexahydrate. 10 mL of this solution complies with the *limit test for iron*, Appendix VII (10 ppm, determined with respect to the content of aluminium chloride hexahydrate).

Ethanol

Not less than 70.0% v/v, Appendix VIII F.

ASSAY

To a weighed quantity containing about 0.4 g of Aluminium Chloride Hexahydrate add 25 mL of *water* and carry out the *complexometric titration of aluminium*, Appendix VIII D. Each mL of *0.1M disodium edetate VS* is equivalent to 24.14 mg of $AlCl_3,6H_2O$.

www.webofpharma.com

https://thuocngocanh.com/

If the declared content is in terms of weight in volume, determine the *weight per mL* of the solution, Appendix V G, and hence calculate the content of $AlCl_3,6H_2O$, weight in volume.

STORAGE

Aluminium Chloride Solution should be stored upright.

LABELLING

The label states that the solution is flammable.

© Crown Copyright 2022

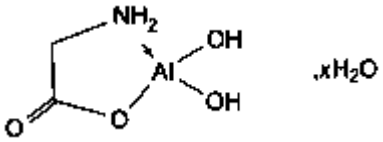
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Glycinate

General Notices



$C_2H_6AlNO_4,xH_2O$ 135.1 *41354-48-7*

Action and use

Antacid.

DEFINITION

Aluminium Glycinate is a basic aluminium monoglycinate, partly hydrated. It contains not less than 34.5% and not more than 38.5% of Al_2O_3 and not less than 9.9% and not more than 10.8% of N, both calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder.

Practically insoluble in *water* and in organic solvents. It dissolves in dilute mineral acids and in aqueous solutions of the alkali hydroxides.

IDENTIFICATION

A. Add 0.1 g to 10 mL of a solution prepared by dissolving 0.84 g of *citric acid* in 8 mL of *1M sodium hydroxide* and diluting to 20 mL with *water*. Add 0.5 mL of a 0.1% w/v solution of *ninhydrin* in *methanol* and warm. A purple colour is produced.

B. Suspend 1 g in 25 mL of *0.5M hydrochloric acid* and heat gently until a clear solution is produced. Reserve half of the solution. To 2 mL of the solution add 0.15 mL of *liquefied phenol*, shake and add carefully without shaking 5 mL of *dilute sodium hypochlorite solution*. A blue colour is produced.

C. The solution reserved in test B yields the reaction characteristic of *aluminium salts,* Appendix VI.

TESTS

Acidity or alkalinity

pH of a suspension of 1 g in 25 mL of *carbon dioxide-free water*, 6.5 to 7.5, Appendix V L.

Neutralising capacity

www.webofpharma.com

https://thuocngocanh.com/

Shake 0.2 g vigorously with 25 mL of *0.1M* *hydrochloric acid* for 5 minutes and allow to stand for 5 minutes. The pH of the mixture is greater than 3.0, Appendix V L.

Arsenic

Dissolve 2.0 g in 18 mL of *brominated hydrochloric acid* and 32 mL of *water*. 25 mL of the resulting solution complies with the *limit test for arsenic*, Appendix VII (1 ppm).

Mercuric salts

Dissolve 2.0 g in 10 mL of *1M* *sulfuric acid*, transfer to a separating funnel with the aid of *water*, dilute to about 50 mL with *water* and add 50 mL of *0.5M* *sulfuric acid*. Add 100 mL of *water*, 2 g of *hydroxylamine hydrochloride*, 1 mL of *0.05M* *disodium edetate* and 1 mL of *glacial acetic acid*. Add 5 mL of *chloroform*, shake, allow to separate and discard the chloroform layer. Titrate the aqueous layer with a solution of *dithizone* in *chloroform* containing 8 µg per mL until the chloroform layer remains green. After each addition, shake vigorously, allow the layers to separate and discard the chloroform layer. Repeat the operation using a solution prepared by diluting 1 mL of *mercury standard solution (5 ppm Hg)* to 100 mL with *0.5M* *sulfuric acid* and beginning at the words 'Add 100 mL of *water*…'. The volume of the dithizone solution required by the substance being examined does not exceed that required by the mercury standard solution.

Chloride

Dissolve 1.0 g in 10 mL of *2M* *nitric acid* and dilute to 100 mL with *water*. 15 mL of the resulting solution complies with the *limit test for chlorides*, Appendix VII (330 ppm).

Loss on drying

When dried to constant weight at 130°, loses not more than 12.0% of its weight. Use 1 g.

ASSAY

For Al_2O_3

Dissolve 0.25 g in a mixture of 3 mL of *1M* *hydrochloric acid* and 50 mL of *water*, add 50 mL of *0.05M* *disodium edetate VS* and neutralise with *1M* *sodium hydroxide* using *methyl red solution* as indicator. Heat the solution to boiling, allow to stand for 10 minutes on a water bath, cool rapidly, add about 50 mg of *xylenol orange triturate* and 5 g of *hexamine* and titrate the excess of disodium edetate with *0.05M* *lead nitrate VS* until the solution becomes red. Each mL of *0.05M* *disodium edetate VS* is equivalent to 2.549 mg of Al_2O_3.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Hydroxide Chewable Tablets

General Notices

Aluminium Hydroxide Tablets

Chewable Aluminium Hydroxide Tablets

DEFINITION

Aluminium Hydroxide Chewable Tablets contain, in each, 500 mg of Dried Aluminium Hydroxide in a suitable basis with a peppermint flavour.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aluminium oxide, Al_2O_3

Not less than the equivalent of 0.225 g.

IDENTIFICATION

The powdered tablets yield the reaction characteristic of *aluminium salts*, Appendix VI.

TESTS

Disintegration

The requirement for Disintegration does not apply to Aluminium Hydroxide Chewable Tablets.

Neutralising capacity

Pass a sufficient quantity of the powder prepared for use in the Assay through a sieve with a nominal mesh aperture of 150 µm. Mix a quantity of the powder containing 0.5 g of Dried Aluminium Hydroxide with a small quantity of *water* to give a smooth paste and slowly add further quantities of *water* to a total volume of 100 mL. Warm to 37°, add 100 mL of *0.1M hydrochloric acid VS* previously heated to 37° and stir continuously, maintaining the temperature at 37°. The pH of the solution at 37° after 10, 15 and 20 minutes is not less than 1.6, 1.8 and 2.2 respectively and at no time during this period is it more than 4.0. Add 10 mL of *0.5M hydrochloric acid VS* previously heated to 37°, stir continuously for 1 hour maintaining the temperature at 37° and titrate the solution with *0.1M sodium hydroxide VS* to pH 3.5. Subtract the volume of *0.1M sodium hydroxide VS* from 150 to obtain the number of mL of *0.1M hydrochloric acid VS* required for the neutralisation. Calculate the number of mL of *0.1M hydrochloric acid VS* required for the total weight of the tablets taken for the Assay and divide by the number of tablets. The result is not less than 115.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Weigh and powder 20 tablets, avoiding frictional heating. Dissolve a quantity of the powder containing 0.4 g of Dried Aluminium Hydroxide as completely as possible in a mixture of 3 mL of *hydrochloric acid* and 3 mL of *water* by warming on a water bath, cool to below 20° and dilute to 100 mL with *water*. To 20 mL of this solution add 40 mL of 0.05M *disodium edetate VS*, 80 mL of *water* and 0.15 mL of *methyl red solution* and neutralise by the drop wise addition of *1M sodium hydroxide VS*. Heat on a water bath for 30 minutes, add 3 g of *hexamine* and titrate with 0.05M *lead nitrate VS* using 0.5 mL of *xylenol orange solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.549 mg of Al_2O_3.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Hydroxide Oral Suspension

General Notices

DEFINITION

Aluminium Hydroxide Oral Suspension is an aqueous suspension of Dried Aluminium Oxide together with varying quantities of basic aluminium carbonate. It contains the equivalent of 4% w/w of aluminium oxide and has a peppermint flavour.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of aluminium oxide, Al_2O_3

The equivalent of 3.5 to 4.4% w/w.

CHARACTERISTICS

A white suspension from which small amounts of clear liquid may separate on standing. It may exhibit thixotropic properties.

IDENTIFICATION

A solution in 2M *hydrochloric acid* yields the reaction characteristic of *aluminium salts*, Appendix VI.

TESTS

Alkalinity

pH, when diluted with an equal volume of *carbon dioxide-free water*, not more than 7.5, Appendix V L.

Neutralising capacity

Disperse 5 g in 100 mL of *water*, heat to 37°, add 100 mL of *0.1M hydrochloric acid VS* previously heated to 37° and stir continuously, maintaining the temperature at 37°. The pH of the solution, at 37°, after 10, 15 and 20 minutes, is not less than 1.8, 2.3 and 3.0 respectively and at no time during this period is it more than 4.0. Add 10 mL of *0.5M hydrochloric acid VS* previously heated to 37°, stir continuously for 1 hour maintaining the temperature at 37° and titrate the solution with *0.1M sodium hydroxide VS* to pH 3.5. Not more than 50 mL of *0.1M sodium hydroxide VS* is required.

Ammonium salts

To 25 g in an ammonia-distillation apparatus add 25 mL of 5M *sodium hydroxide* and 250 mL of *water*, distil about 100 mL, collecting the distillate in 25 mL of *0.1M hydrochloric acid VS*, and titrate the excess of acid with *0.1M sodium hydroxide VS* using *methyl red solution* as indicator. Not less than 20.0 mL of *0.1M sodium hydroxide VS* is required.

Arsenic

www.webofpharma.com

https://thuocngocanh.com/

Arsenic

Dissolve 2.0 g in 18 mL of *brominated hydrochloric acid* and 32 mL of *water*. 25 mL of the resulting solution complies with the *limit test for arsenic*, Appendix VII (1 ppm).

Chloride

Dissolve 0.30 g in 2 mL of 2M *nitric acid*, boil, cool, dilute to 250 mL with *water* and filter. 15 mL of the filtrate complies with the *limit test for chlorides*, Appendix VII (0.3%).

Sulfate

Dissolve 0.50 g in 5 mL of 2M *hydrochloric acid*, boil, cool, dilute to 200 mL with *water* and filter. 12.5 mL of the filtrate, diluted to 15 mL with 2M *hydrochloric acid*, complies with the *limit test for sulfates*, Appendix VII (0.5%).

Microbial contamination

Carry out a quantitative evaluation for Enterobacteria and certain other Gram-negative bacteria, Appendix XVI B1. 0.01 mL of the preparation gives a negative result, Table I (most probable number of bacteria per gram fewer than 10^2).

ASSAY

Dissolve 5 g in 3 mL of *hydrochloric acid* by warming on a water bath, cool to below 20° and dilute to 100 mL with *water*. To 20 mL of this solution add 40 mL of 0.05M *disodium edetate VS*, 80 mL of *water* and 0.15 mL of *methyl red solution* and neutralise by the drop wise addition of 1M *sodium hydroxide*. Heat on a water bath for 30 minutes, add 3 g of *hexamine* and titrate with 0.05M *lead nitrate VS* using 0.5 mL of *xylenol orange solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.549 mg of Al_2O_3.

STORAGE

Aluminium Hydroxide Oral Suspension should be kept at a temperature not exceeding 30°. It should not be allowed to freeze.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Magnesium Silicate

General Notices

(Ph. Eur. monograph 1388)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of colloidal-size particles of montmorillonite and saponite, practically free from grit and non-swellable ore.

The requirements for viscosity and ratio of aluminium content to magnesium content differ for the several types of aluminium magnesium silicate, as shown in the table below.

Type	Viscosity (mPa·s)		Al content / Mg content	
	min.	max.	min.	max.
IA	225	600	0.5	1.2
IB	150	450	0.5	1.2
IC	800	2200	0.5	1.2
IIA	100	300	1.4	2.8

CHARACTERS

Appearance

Almost white, coarse powder, granules or flakes (types IA, IC and IIA); almost white, fine powder (type IB).

Solubility

Practically insoluble in water and in organic solvents.

It swells in water to produce a colloidal dispersion.

IDENTIFICATION

Carry out either tests A, B, C, F or tests D, E.

www.webofpharma.com

https://thuocngocanh.com/

A. In a platinum crucible mix 1.0 g with 5.0 g of *anhydrous lithium metaborate R*. Heat slowly at first and ignite at 1000-1200 °C for 15 min. Allow to cool and crush the residue. 0.25 g of the residue gives the reaction of silicates (*2.3.1*).

B. Dissolve 1.0 g of the residue obtained in identification test A in a mixture of 5 mL of *dilute hydrochloric acid R* and 10 mL of *water R*. Filter to obtain a clear solution and add *ammonium chloride buffer solution pH 10.0 R*. A white, gelatinous precipitate is formed. Centrifuge and keep the supernatant for identification test C. Dissolve the precipitate in *dilute hydrochloric acid R*. Add dropwise *dilute sodium hydroxide solution R*. A white gelatinous precipitate is formed. Filter and add a few drops of *phenolphthalein solution R* to the residue. The residue turns pink. Wash the residue with *water R* until the pink colour is completely discharged and the residue remains white upon addition of a drop of *phenolphthalein solution R*. Sprinkle a few crystals of *sodium fluoride R* on the residue. The residue, in contact with the crystals, turns pink again in a short time.

C. To 2 mL of the supernatant obtained after centrifugation in identification test B, add 1 mL of *dilute ammonia R1* and 1 mL of *ammonium chloride solution R*. Upon the addition of *dilute ammonia R1* a white precipitate may form, which dissolves after addition of the *ammonium chloride solution R*. Add 1 mL of *disodium hydrogen phosphate solution R*. A white precipitate is formed.

D. X-ray diffraction (*2.9.33*), oriented sample.

Add 2 g in small portions to 100 mL of *water R*, with vigorous shaking. Allow to stand for at least 12 h to ensure complete hydration. Place 2 mL of the resulting mixture on a suitable glass slide and allow to dry in air at room temperature to produce an oriented film. Place the slide in a vacuum desiccator over *ethylene glycol R*. Evacuate the desiccator and close the stopcock so that the ethylene glycol saturates the chamber. Allow to stand for at least 12 h. Record the X-ray diffraction pattern and calculate the *d* values: the largest peak corresponds to a *d* value between 1.5 nm and 1.72 nm.

E. X-ray diffraction (*2.9.33*), random sample.

Prepare a random powder sample, record the X-ray diffraction pattern and determine the *d* values in the region between 0.148 nm and 0.154 nm. Peaks are found between 0.1492 nm and 0.1504 nm and between 0.1510 nm and 0.1540 nm.

F. It complies with the limits of the assay.

TESTS

pH (*2.2.3*)

9.0 to 10.0.

Disperse 5.0 g in 100 mL of *carbon dioxide-free water R*.

Viscosity (*2.2.10*)

Weigh a quantity of the substance to be examined equivalent to 25.0 g of the dried substance and immediately transfer to a suitable 1 L blender jar containing a quantity of *water R*, at 25 ± 2 °C, that is sufficient to produce a mixture weighing 500 g. Blend for exactly 3 min, at 14 000-15 000 r/min. The heat generated during blending causes the temperature to rise to above 30 °C. Transfer the contents of the blender to a 600 mL beaker and allow to stand for 5 min. The sample temperature should be 33 ± 3 °C.

Using a suitable rotating viscometer equipped with a spindle as specified below, operate the viscometer at 60 r/min for exactly 6 min and record the scale reading.

www.webofpharma.com

https://thuocngocanh.com/

For type IA, use a spindle with a cylinder 1.87 cm in diameter and 0.69 cm high attached to a shaft 0.32 cm in diameter, the distance from the top of the cylinder to the lower tip of the shaft being 2.54 cm, and an immersion depth of 5.00 cm (No. 2 spindle); if the scale reading is greater than 90 per cent of the full scale, repeat the measurement using a spindle similar to the No. 2 spindle but with a cylinder 1.27 cm in diameter and 0.16 cm high (No. 3 spindle).

For type IC, use a No. 3 spindle; if the scale reading is greater than 90 per cent of the full scale, repeat the measurement using a spindle with a cylindrical shaft 0.32 cm in diameter and an immersion depth of 4.05 cm (No. 4 spindle).

For types IB and IIA, use a No. 2 spindle.

Limits:

Type	Viscosity (mPa·s)	
	min.	max.
IA	225	600
IB	150	450
IC	800	2200
IIA	100	300

Acid demand

Weigh a quantity of the substance to be examined equivalent to 5.00 g of the dried substance and disperse in 500 mL of *water R* using a suitable blender fitted with a 1 L jar. With constant mixing, add 3.0 mL portions of *0.1 M hydrochloric acid* at 5 s, 65 s, 125 s, 185 s, 245 s, 305 s, 365 s, 425 s, 485 s, 545 s, 605 s, 665 s and 725 s and add a 1.0 mL portion at 785 s. The pH (*2.2.3*) determined at 840 s is not greater than 4.0.

Arsenic (*2.4.2, Method A*)

Maximum 3 ppm.

Transfer 16.6 g to a 250 mL beaker containing 100 mL of *dilute hydrochloric acid R*. Mix, cover with a watch glass and boil gently, with occasional stirring, for 15 min. Allow the insoluble matter to settle and decant the supernatant through a rapid-flow filter paper into a 250 mL volumetric flask, retaining as much sediment as possible in the beaker. To the residue in the beaker add 25 mL of hot *dilute hydrochloric acid R*, stir, heat to boiling, allow the insoluble matter to settle and decant the supernatant through the filter into the volumetric flask. Repeat the extraction with 4 additional quantities, each of 25 mL, of hot *dilute hydrochloric acid R*, decanting each supernatant through the filter into the volumetric flask. At the last extraction, transfer as much of the insoluble matter as possible onto the filter. Allow the combined filtrates to cool to room temperature and dilute to 250.0 mL with *dilute hydrochloric acid R*. Dilute 5.0 mL of this solution to 25.0 mL with *dilute hydrochloric acid R*.

Lead

Maximum 15 ppm.

www.webofpharma.com

https://thuocngocanh.com/

Atomic absorption spectrometry (2.2.23, Method I).

Test solution Transfer 10.0 g to a 250 mL beaker containing 100 mL of *dilute hydrochloric acid R*. Mix, cover with a watch glass and boil for 15 min. Allow to cool to room temperature and allow the insoluble matter to settle. Decant the supernatant through a rapid-flow filter paper into a 400 mL beaker. To the insoluble matter in the 250 mL beaker add 25 mL of hot *water R*. Stir, allow the insoluble matter to settle and decant the supernatant through the filter into the 400 mL beaker. Repeat the extraction with 2 additional quantities, each of 25 mL, of *water R*, decanting each time the supernatant through the filter into the 400 mL beaker. Wash the filter with 25 mL of hot *water R*, collecting this filtrate in the 400 mL beaker. Concentrate the combined filtrates to about 20 mL by gently boiling. If a precipitate appears, add about 0.1 mL of *nitric acid R*, heat to boiling and allow to cool to room temperature. Filter the concentrated extracts through a rapid-flow filter paper into a 50 mL volumetric flask. Transfer the remaining contents of the 400 mL beaker through the filter paper and into the flask with *water R*. Dilute this solution to 50.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *lead standard solution (10 ppm Pb) R*, diluted as necessary with *water R*.

Source Lead hollow-cathode lamp.

Wavelength 217 nm.

Atomisation device Oxidising air-acetylene flame.

Loss on drying (2.2.32)

Maximum 8.0 per cent, determined on 1.000 g by drying in an oven at 110 °C.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

ASSAY

Aluminium

Atomic absorption spectrometry (2.2.23, Method I).

Test solution In a platinum crucible mix 0.200 g with 1.0 g of *anhydrous lithium metaborate R*. Heat slowly at first and ignite at 1000-1200 °C for 15 min. Allow to cool, place the crucible in a 100 mL beaker containing 25 mL of a 40 per cent *V/V* solution of *dilute nitric acid R* and add 50 mL of a 40 per cent *V/V* solution of *dilute nitric acid R*, filling and submerging the crucible. Place a polytetrafluoroethylene-coated magnetic stirring bar in the crucible and stir gently with a magnetic stirrer until dissolution is complete. Transfer the solution to a 200 mL volumetric flask, wash the beaker, crucible and magnetic stirrer bar with *water R*, collecting the washings in the volumetric flask, and dilute to 200.0 mL with *water R* (solution A). To 20.0 mL of solution A add 20 mL of a 10 g/L solution of *sodium chloride R* and dilute to 100.0 mL with *water R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions Dissolve, with gentle heating, 1.000 g of *aluminium R* in a mixture of 10 mL of *hydrochloric acid R* and 10 mL of *water R*. Allow to cool, then dilute to 1000.0 mL with *water R* (1 mg of aluminium per millilitre). Into 4 identical volumetric flasks, each containing 0.20 g of *sodium chloride R*, introduce 1.0 mL, 2.0 mL, 3.0 mL and 4.0 mL of this solution respectively, and dilute to 100.0 mL with *water R*.

Blank solution Dissolve 0.20 g of *sodium chloride R* in *water R* and dilute to 100.0 mL with the same solvent.

Source Aluminium hollow-cathode lamp.

Wavelength 309 nm.

Atomisation device Acetylene-nitrous oxide flame.

Magnesium

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 25.0 mL of solution A, prepared in the assay for aluminium, to 50.0 mL with *water R*. To 5.0 mL of this solution add 20.0 mL of *lanthanum chloride solution R* and dilute to 100.0 mL with *water R*.

Reference solutions Place 1.000 g of *magnesium R* in a 250 mL beaker containing 20 mL of *water R* and carefully add 20 mL of *hydrochloric acid R*, warming if necessary to dissolve. Transfer the solution to a volumetric flask and dilute to 1000.0 mL with *water R* (1 mg of magnesium per millilitre). Dilute 5.0 mL of this solution to 500.0 mL with *water R*. Into 4 identical volumetric flasks, introduce 5.0 mL, 10.0 mL, 15.0 mL and 20.0 mL of the solution respectively. To each flask add 20.0 mL of *lanthanum chloride solution R* and dilute to 100.0 mL with *water R*.

Blank solution Dilute 20 mL of *lanthanum chloride solution R* to 100.0 mL with *water R*.

Source Magnesium hollow-cathode lamp.

Wavelength 285 nm.

Atomisation device Air-acetylene flame.

LABELLING

The label states the ratio of aluminium content to magnesium content, the viscosity and the corresponding type (see Definition).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the

www.webofpharma.com

https://thuocngocanh.com/

purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for aluminium magnesium silicate used as viscosity-increasing agent and stabiliser.

Viscosity

(see Tests).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Phosphate Gel

General Notices

(Ph. Eur. monograph 2166)

Action and use

Antacid; vaccine adjuvant.

Ph Eur

DEFINITION

Hydrated $AlPO_4$ in gel form.

Content

19.0 per cent to 21.0 per cent of $AlPO_4$.

CHARACTERS

Appearance

Gel.

Solubility

Practically insoluble in water, in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute solutions of mineral acids.

IDENTIFICATION

A. Solution S (see Tests) gives reaction (b) of phosphates (*2.3.1*).

B. Solution S gives the reaction of aluminium (*2.3.1*).

C. It complies with the assay.

TESTS

Solution S

Dissolve 2.00 g in *dilute hydrochloric acid R* and dilute to 100 mL with the same acid.

pH (*2.2.3*)

6.0 to 8.0.

www.webofpharma.com

https://thuocngocanh.com/

Peroxides

Maximum 150 ppm, expressed as hydrogen peroxide.

Test solution Dissolve with heating 1.0 g of the substance to be examined in 5 mL of *dilute hydrochloric acid R*, then add 5 mL of *water R* and 2 mL of *divanadium pentoxide solution in sulfuric acid R*.

Reference solution Dilute 1.0 mL of *dilute hydrogen peroxide solution R* to 200.0 mL with *water R*. To 1 mL of this solution add 9 mL of *water R* and 2 mL of *divanadium pentoxide solution in sulfuric acid R*.

The test solution is not more intensely coloured than the reference solution.

Chlorides (*2.4.4*)

Maximum 500 ppm.

Dissolve 1.3 g in 5 mL of *dilute nitric acid R* and dilute to 200 mL with *water R*.

Soluble phosphates

Maximum 0.5 per cent, expressed as PO_4.

Test solution Centrifuge 10.0 g until a clear supernatant is obtained. To 2.00 mL of the supernatant add 20.0 mL of a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with *water R*. To 10.0 mL of this solution add 10.0 mL of nitro-molybdovanadic reagent R and dilute to 50.0 mL with *water R*. Allow to stand protected from light for 15 min.

Reference solution Add 10.0 mL of nitro-molybdovanadic reagent R to 10.0 mL of a 143 mg/L solution of *potassium dihydrogen phosphate R* and dilute to 50.0 mL with *water R*. Allow to stand protected from light for 15 min.

Measure the absorbances (*2.2.25*) of the 2 solutions at 400 nm. The absorbance of the test solution is not greater than that of the reference solution.

Sulfates (*2.4.13*)

Maximum 0.2 per cent.

Dilute 25 mL of solution S to 100 mL with *distilled water R*.

Soluble aluminium

Maximum 50 ppm.

To 16.0 g add 50 mL of *water R*. Heat to boiling for 5 min. Cool and centrifuge. Separate the supernatant. Wash the residue with 20 mL of *water R* and centrifuge. Separate the supernatant and add to the first supernatant. To the combined supernatants add 5 mL of *hydrochloric acid R* and 20 mL of *water R*. Introduce all of this solution into a 500 mL conical flask and carry out the complexometric titration of aluminium (*2.5.11*) using *0.01 M sodium edetate*.

Arsenic (*2.4.2, Method A*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 1 ppm, determined on 1.0 g.

Acid neutralising capacity

Add 2.0 g to 30 mL of *0.1 M hydrochloric acid* heated to 37 °C and maintain at 37 °C while shaking. Determine the pH after 15 min. The pH (2.2.3) of the mixture is 2.0 to 2.5.

Residue on ignition

19.0 per cent to 23.0 per cent.

Heat 0.500 g at 50 °C for 5 hours, then ignite at 500 ± 50 °C until constant mass.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of bile-tolerant gram-negative bacteria (2.6.13).

Absence of *Escherichia coli* (2.6.13).

ASSAY

Dissolve with heating 0.300 g in 5 mL of *dilute hydrochloric acid R*. Add 45 mL of *water R*, 10.0 mL of *0.1 M sodium edetate* and 30 mL of a mixture of equal volumes of *ammonium acetate solution R* and *dilute acetic acid R*. Heat to boiling and maintain boiling for 3 min. Cool, then add 25 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M zinc sulfate*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M zinc sulfate* is equivalent to 12.2 mg of $AlPO_4$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Powder

General Notices

Al 26.98 *7429-90-5*

Action and use

Topical protective.

Preparation

Compound Aluminium Paste

DEFINITION

Aluminium Powder consists mainly of metallic aluminium in the form of very small flakes, usually with an appreciable proportion of aluminium oxide; it is lubricated with stearic acid to prevent oxidation. It contains not less than 86.0% of Al, calculated with reference to the substance freed from lubricant and volatile matter.

CHARACTERISTICS

A silvery grey powder.

Practically insoluble in *water* and in *ethanol (96%)*. It dissolves in dilute acids and in aqueous solutions of alkali hydroxides, with the evolution of hydrogen.

IDENTIFICATION

A solution in *2M hydrochloric acid* yields the reaction characteristic of *aluminium salts*, Appendix VI.

TESTS

Surface-covering power

Not less than 4000 cm^2 per g when determined by the following method. Fill with *water* a shallow trough measuring approximately 60 cm × 12 cm × 1.5 cm, fitted with a movable partition so constructed that it is a sliding fit and can be used to divide the trough into two rectangular areas. Place the movable partition near one end and sprinkle 50 mg of the substance being examined on the surface of the liquid confined in the smaller area. Using a glass rod, spread the powder evenly over the liquid surface until an unbroken film covers the entire surface. Move the partition so as to increase the area confined and again spread the powder to cover the increased surface. Continue this process and determine the maximum unbroken surface area obtained. The surface-covering power is the area covered per g of the powder at the breaking point of the film.

.

www.webofpharma.com

https://thuocngocanh.com/

Iron

Dissolve 10 mg in 20 mL of *2M* *hydrochloric acid* and dilute to 100 mL with *water*. 10 mL of the resulting solution complies with the *limit test for iron*, Appendix VII (1.0%).

Lead

Use two solutions prepared in the following manner. For solution (1) boil 0.40 g with 20 mL of *2M* *hydrochloric acid* and 10 mL of *water* until effervescence ceases, add 0.5 mL of *nitric acid*, boil for 30 seconds and cool; add 2 g of *ammonium chloride* and 2 g of *ammonium thiocyanate*, extract with three 10 mL quantities of a mixture of equal volumes of *amyl* *alcohol* and *ether*, discard the extracts and add 2 g of *citric acid*. For solution (2) dissolve 2 g of *citric acid* in 10 mL of *2M hydrochloric acid* and add 4 mL of *lead standard solution (10 ppm Pb)*. Make solutions (1) and (2) alkaline with 5M *ammonia* and to each add 1 mL of *potassium cyanide solution PbT*. The solutions should be not more than faintly opalescent. If the colours of the solutions differ, equalise by the addition of about 0.2 mL of a highly diluted solution of burnt sugar or other non-reactive substance. Dilute each solution to 50 mL with *water*, add 0.1 mL of a 10% w/v solution of *sodium sulfide* to each and mix thoroughly. The colour produced in solution (1) is not more intense than that produced in solution (2), when viewed against a white background (100 ppm).

Other metals

Dissolve 2 g in 40 mL of *2M hydrochloric acid*. Dilute 20 mL of the solution to 100 mL with *water*, make alkaline to *litmus paper* by the addition of 5M *ammonia*, boil and filter. Evaporate the filtrate to dryness, add 0.05 mL of *sulfuric acid* and ignite. The residue weighs not more than 2 mg.

Lubricant

To 2 g add 100 mL of hot *water*, cover and add, drop wise, sufficient of a mixture of equal volumes of *hydrochloric acid* and *water* to dissolve the metal almost completely. Heat to complete dissolution, cool, filter through a hardened filter paper and wash the vessel and filter paper thoroughly with *water*; dry both the vessel and paper at room temperature. Extract the paper with three 100-mL quantities of boiling, freshly distilled *acetone*, using the original vessel to contain the solvent and then wash the paper with five 10-mL quantities of freshly distilled *acetone*. Evaporate the combined filtrate and washings to dryness using a rotary evaporator. The residue, after drying at 105° for 30 minutes and allowing to cool, weighs 10 to 60 mg.

When the basin containing the residue is floated in a beaker of water suitably stirred and heated, the residue melts between 40° and 60°. The residue is almost completely soluble, with effervescence, in hot *dilute sodium carbonate solution*.

Volatile matter

When heated to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

ASSAY

Transfer 0.2 g, previously freed from lubricant by successive washing with *acetone* and drying, to a three-necked 500 mL flask fitted with a 150 mL dropping funnel, an inlet tube connected to a cylinder of *carbon dioxide* and an outlet tube dipping into a water trap. Add 60 mL of *water* and disperse the substance being examined; replace the air by *carbon dioxide* and add 100 mL of a solution containing 56 g of *ammonium iron(III) sulfate* and 7.5 mL of *sulfuric acid* in *water*. While maintaining an atmosphere of *carbon dioxide* in the flask, heat to boiling, boil for 5 minutes after the sample has dissolved, cool rapidly to 20° and dilute to 250 mL with *water*. To 50 mL add 15 mL of

www.webofpharma.com

https://thuocngocanh.com/

orthophosphoric acid and titrate with 0.02M *potassium permanganate VS*. Each mL of 0.02M *potassium permanganate VS* is equivalent to 0.8994 mg of Al.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Sodium Silicate

General Notices

(Ph. Eur. monograph 1676)

Ph Eur

DEFINITION

Silicic acid aluminium sodium salt of synthetic origin.

Content

— *aluminium* (Al; M_r 26.98): 2.7 per cent to 7.9 per cent (dried substance);

— *sodium* (Na; M_r 22.99): 3.7 per cent to 6.3 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, fine, light, amorphous powder.

Solubility

Practically insoluble in water and in organic solvents.

IDENTIFICATION

A. Transfer 1.0 g to a 100 mL beaker and add 10 mL of *dilute hydrochloric acid R*. Mix, cover with a watch glass and boil for 15 min. Allow to cool to room temperature, mix and centrifuge the solution. 2 mL of the supernatant gives the reaction of aluminium (*2.3.1*).

B. 2 mL of the supernatant obtained in identification test A gives reaction (a) of sodium (*2.3.1*).

C. 0.2 g gives the reaction of silicates (*2.3.1*).

TESTS

pH (*2.2.3*)

9.5 to 11.5.

Disperse 5.0 g in 100 mL of *carbon dioxide-free water R*.

Arsenic (*2.4.2, Method A*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 3 ppm.

Transfer 8.3 g to a 250 mL beaker containing 50 mL of *dilute hydrochloric acid R*. Mix, cover with a watch glass and boil gently, with occasional stirring, for 15 min. Centrifuge, and decant the supernatant through a rapid-flow filter paper into a 250 mL volumetric flask. To the residue in the beaker, add 25 mL of hot *dilute hydrochloric acid R*, stir, centrifuge, and decant the supernatant through the same filter into the volumetric flask. Repeat the extraction with 3 additional quantities, each of 25 mL, of hot *dilute hydrochloric acid R*, filtering each supernatant through this filter into the volumetric flask. Allow the combined filtrates to cool to room temperature and dilute to 250.0 mL with *dilute hydrochloric acid R*. Dilute 10.0 mL of the solution to 25.0 mL with *water R*.

Lead

Maximum 5 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Transfer 5.0 g to a 250 mL beaker containing 50 mL of *dilute hydrochloric acid R*. Mix, cover with a watch glass and boil for 15 min. Allow to cool to room temperature. Centrifuge, and decant the supernatant through a rapid-flow filter paper into a 250 mL beaker. To the insoluble matter add 25 mL of hot *water R*. Stir vigorously, centrifuge, and decant the supernatant through the same filter into the beaker. Repeat the extraction with 2 additional quantities, each of 25 mL, of hot *water R*, decanting each supernatant through the filter into the beaker. Wash the filter with 25 mL of hot *water R*, collecting the filtrate in the beaker. Concentrate the combined filtrates by gently boiling to about 15 mL. Add about 0.05 mL of *heavy metal-free nitric acid R*, heat to boiling and allow to cool to room temperature. Filter the concentrated extracts through a rapid-flow filter paper into a 25 mL volumetric flask. Transfer the remaining contents of the beaker through the filter paper and into the volumetric flask with *water R* and dilute to 25.0 mL with the same solvent.

Reference solutions Into 4 separate 100 mL volumetric flasks, introduce respectively 3.0 mL, 5.0 mL, 10.0 mL and 15.0 mL of *lead standard solution (10 ppm Pb) R*, add 0.20 mL of *heavy metal-free nitric acid R* and dilute to 100.0 mL with *water R*.

Source Lead hollow-cathode lamp.

Wavelength 217.0 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 8.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Loss on ignition

5.0 per cent to 11.0 per cent (dried substance), determined on 1.000 g by ignition in a platinum crucible to constant mass at 1000 ± 25 °C.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

www.webofpharma.com

https://thuocngocanh.com/

Absence of *Escherichia coli* (2.6.13).

ASSAY

Aluminium

Atomic absorption spectrometry (2.2.23, Method I).

Acid mixture Add 50 mL of *nitric acid R* to 500 mL of *water R*. Dissolve in this solution 17 g of *tartaric acid R* and dilute to 1000 mL with *water R*.

Blank solution Dissolve 1.4 g of *anhydrous lithium metaborate R* in 60 mL of the acid mixture and dilute to 200 mL with *water R*.

Test solution In a platinum crucible mix 0.200 g with 1.4 g of *anhydrous lithium metaborate R*. Heat slowly at first and ignite at 1100 ± 25 °C for 15 min. Cool, then place the crucible in a 100 mL beaker containing 60 mL of the acid mixture. Place a polytetrafluoroethylene-coated magnetic stirring bar in the crucible and stir gently with a magnetic stirrer for 16 h. Transfer the contents of the crucible into a 200 mL volumetric flask. Wash the crucible, the magnetic stirring bar and the beaker with *water R* and dilute to 200.0 mL with the same solvent (solution A). To 10.0 mL of this solution, add 1.0 mL of *lanthanum chloride solution R* and dilute to 50.0 mL with *water R*.

Reference solutions Into 5 separate 50 mL volumetric flasks, introduce respectively 1.0 mL, 2.5 mL, 5.0 mL, 7.5 mL and 10.0 mL of *aluminium standard solution (100 ppm Al) R*, add 1 mL of *lanthanum chloride solution R* and 10 mL of the blank solution, and dilute to 50.0 mL with *water R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Acetylene-nitrous oxide flame.

Sodium

Atomic emission spectrometry (2.2.22, Method I).

Test solution To 2.0 mL of solution A, prepared in the assay of aluminium, add 1 mL of a 12.5 g/L solution of *caesium chloride R* and dilute to 20.0 mL with *water R*.

Reference solutions Into 5 separate 200 mL volumetric flasks, each containing 10 mL of a 12.5 g/L solution of *caesium chloride R*, introduce respectively 1.0 mL, 2.0 mL, 4.0 mL, 6.0 mL and 10.0 mL of *sodium standard solution (200 ppm Na) R* and dilute to 200.0 mL with *water R*.

Wavelength 589.0 nm.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Stearate

General Notices

(Ph. Eur. monograph 1663)

Ph Eur

DEFINITION

Aluminium salts of a mixture of solid organic acids consisting mainly of variable proportions of aluminium stearate [$(C_{17}H_{35}COO)_3Al$; M_r 877] and aluminium palmitate [$(C_{15}H_{31}COO)_3Al$; M_r 793]. The organic acids are obtained from sources of vegetable or animal origin.

Content

— *aluminium* (Al; A_r 26.98): 3.0 per cent to 9.0 per cent (dried substance);

— *stearic acid in the fatty acid fraction*: minimum 35.0 per cent;

— *sum of stearic acid and palmitic acid in the fatty acid fraction*: minimum 90.0 per cent.

CHARACTERS

Appearance

White or almost white, very fine, light powder.

Solubility

Practically insoluble in water and in anhydrous ethanol.

IDENTIFICATION

First identification: C, D.

Second identification: A, B, D.

A. Freezing point (*2.2.18*): minimum 53 °C, determined on the residue obtained in the preparation of solution S (see Tests).

B. Acid value (*2.5.1*): 195 to 210.

Dissolve 0.200 g of the residue obtained in the preparation of solution S in 25 mL of the prescribed mixture of solvents.

C. Examine the chromatograms obtained in the assay of stearic acid and palmitic acid.

www.webofpharma.com

https://thuocngocanh.com/

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the 2 principal peaks in the chromatogram obtained with the reference solution.

D. 1 mL of solution S gives the reaction of aluminium (2.3.1). The addition of 0.5 mL of *dilute hydrochloric acid R* described in the general method is omitted.

TESTS

Solution S

To 5.0 g add 50 mL of *peroxide-free ether R*, 20 mL of *dilute nitric acid R* and 20 mL of *distilled water R* and heat gently under a reflux condenser until dissolution is complete. Allow to cool. In a separating funnel, separate the aqueous layer and shake the ether layer with 2 quantities, each of 4 mL, of *distilled water R*. Combine the aqueous layers, wash with 15 mL of *peroxide-free ether R* and dilute to 50.0 mL with *distilled water R* (solution S). Evaporate the ether layer to dryness and dry the residue at 100-105 °C. Keep the residue for identification tests A and B.

Acidity or alkalinity

To 1.0 g add 20 mL of *carbon dioxide-free water R* and boil for 1 min with continuous shaking. Cool and filter. To 10 mL of the filtrate add 0.05 mL of *bromothymol blue solution R4*. Not more than 0.05 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (2.4.4)

Maximum 0.1 per cent.

Dilute 0.5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 0.5 per cent.

Dilute 0.3 mL of solution S to 15 mL with *distilled water R*.

Loss on drying (2.2.32)

Maximum 6.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Aluminium

To 0.250 g in a 250 mL conical flask add 20 mL of *methanol R* and, slowly, 2 mL of *sulfuric acid R*. Heat the solution for 30 min under reflux on a water-bath, swirling frequently. Allow to cool. Add 100 mL of *water R* and adjust to about pH 1 by adding approximately 12 mL of *dilute sodium hydroxide solution R*. Add 20.0 mL of *0.1 M sodium edetate* and adjust to between pH 5 and pH 6 by the addition of *sodium acetate R*. Add 70 mg of *xylenol orange triturate R* and titrate immediately and quickly with *0.1 M zinc sulfate* until the colour changes from yellow to pinkish-violet.

1 mL of *0.1 M sodium edetate* is equivalent to 2.698 mg of Al.

Stearic acid and palmitic acid

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution In a conical flask fitted with a reflux condenser, dissolve 0.100 g of the substance to be examined in 5 mL of *boron trifluoride-methanol solution R*. Boil under a reflux condenser for 10 min. Add 4 mL of *heptane R* through the condenser and boil again under a reflux condenser for 10 min. Allow to cool. Add 20 mL of *saturated sodium chloride solution R*. Shake and allow the layers to separate. Dry the organic layer over 0.1 g of *anhydrous sodium sulfate R* previously washed with *heptane R*. Dilute 1.0 mL of the solution to 10.0 mL with *heptane R*.

Reference solution Prepare the reference solution in the same manner as the test solution using 50 mg of *palmitic acid CRS* and 50 mg of *stearic acid CRS* instead of the substance to be examined.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.4 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	70
	2 - 36	70 → 240
	36 - 41	240

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Injection port		220
Detector		260

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to methyl stearate: methyl palmitate = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to methyl palmitate and methyl stearate;

— *repeatability*: maximum relative standard deviation of 3.0 per cent for the areas of the peaks due to methyl palmitate and methyl stearate, determined on 6 injections; maximum relative standard deviation of 1.0 per cent for the ratio of the areas of the peaks due to methyl palmitate to the areas of the peaks due to methyl stearate, determined on 6 injections.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aluminium Sulfate

General Notices

Aluminium Sulphate

(Ph. Eur. monograph 0165)

$Al_2(SO_4)_3,xH_2O$ 342.1 (anhydrous substance)

Preparation

Aluminium Acetate Ear Drops

Ph Eur

DEFINITION

Content

51.0 per cent to 59.0 per cent of $Al_2(SO_4)_3$.

It contains a variable quantity of water of crystallisation.

CHARACTERS

Appearance

Colourless, lustrous crystals or crystalline masses.

Solubility

Soluble in cold water, freely soluble in hot water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives reaction (a) of sulfates (*2.3.1*).

B. Solution S gives the reaction of aluminium (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *water R* and dilute to 50 mL with the same solvent.

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

2.5 to 4.0.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Alkali and alkaline-earth metals

Maximum 0.4 per cent.

To 20 mL of solution S add 100 mL of *water R*, heat and add 0.1 mL of *methyl red solution R*. Add *dilute ammonia R1* until the colour of the indicator changes to yellow. Dilute to 150 mL with *water R*, heat to boiling and filter. Evaporate 75 mL of the filtrate to dryness on a water-bath and ignite. The residue weighs a maximum of 2 mg.

Ammonium (*2.4.1*)

Maximum 500 ppm.

Dilute 0.4 mL of solution S to 14 mL with *water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

Dilute 2 mL of solution S to 10 mL with *water R*. Use 0.3 mL of *thioglycollic acid R* in this test.

ASSAY

Dissolve 0.500 g in 20 mL of *water R*. Carry out the complexometric titration of aluminium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 17.11 mg of $Al_2(SO_4)_3$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alverine Capsules

General Notices

Action and use

Smooth muscle relaxant; antispasmodic.

DEFINITION

Alverine Capsules contain Alverine Citrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of alverine citrate, $C_{20}H_{27}N,C_6H_8O_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.12 g of Alverine Citrate with 5 mL of *methanol* for 5 minutes, filter through a 0.45-µm PTFE filter, evaporate the filtrate to dryness under a stream of nitrogen using a warm water bath and dry the residue for 1 hour at 50° under vacuum. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of alverine citrate (*RS 409*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 20-mL sample of the medium and filter through a 0.45-µm filter, discarding the first 10 mL of the filtrate. Dilute, if necessary, with 0.1M *hydrochloric acid* to produce a solution expected to contain about 0.006% w/v of Alverine Citrate.

(2) 0.006% w/v of *alverine citrate BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of alverine citrate, $C_{20}H_{27}N,C_6H_8O_7$, in the medium from the chromatograms obtained and using the declared content of $C_{20}H_{27}N,C_6H_8O_7$ in *alverine citrate BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 80 mL of *methanol* to a quantity of the mixed contents of the capsules containing 0.6 g of Alverine Citrate. Mix with the aid of ultrasound for 1 hour, allow to cool to room temperature, add sufficient *methanol* to produce 100 mL, mix and filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol* and dilute 1 volume of the resulting solution to 5 volumes with *methanol*.

(3) *alverine citrate impurity standard solution BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of alverine.

MOBILE PHASE

0.01M *sodium dodecyl sulfate* in a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*, adjusting the pH of the mixture to 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *alverine citrate impurity standard solution BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to alverine citrate impurity A, is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.2%);

the area of any peak corresponding to alverine citrate impurity C is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.5%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to alverine citrate impurity D is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (1.4%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the mixed contents of the capsules containing 0.6 g Alverine Citrate add 100 mL of *methanol*, mix with the aid of ultrasound for 1 hour and add sufficient *methanol* to produce 500 mL. Stir vigorously for 10 minutes and filter (Cellulose nitrate filter 0.45 µm is suitable). Dilute 1 volume of the filtrate to 2 volumes with *water*.
(2) Dilute 1 volume of a 0.6% w/v solution of *alverine citrate BPCRS* in *methanol* to 10 volumes with *water*.
(3) *alverine citrate impurity standard solution BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained closely resembles the reference chromatogram supplied with *alverine citrate impurity standard solution BPCRS*.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{27}N,C_6H_8O_7$ in the capsules using the declared content of $C_{20}H_{27}N,C_6H_8O_7$ in *alverine citrate BPCRS*.

STORAGE

Alverine Capsules should be stored in a dry place and not above 25^{o}.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C and D listed under Alverine Citrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

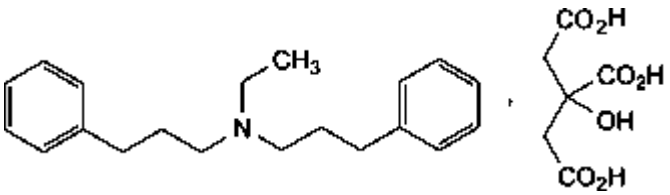
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Alverine Citrate

General Notices

(Ph. Eur. monograph 2156)



$C_{26}H_{35}NO_7$ 473.6 *5560-59-8*

Action and use

Smooth muscle relaxant; antispasmodic.

Preparation

Alverine Capsules

Ph Eur

DEFINITION

N-Ethyl-3-phenyl-*N*-(3-phenylpropyl)propan-1-amine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water and in methylene chloride, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *alverine citrate CRS*.

TESTS

pH (*2.2.3*)

3.5 to 4.5.

Dissolve 0.250 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure. *Use freshly prepared solutions.*

Test solution Dissolve 0.250 g of the substance to be examined in *water R* and dilute to 20 mL with the same solvent. Add 2 mL of *concentrated ammonia R* and shake with 3 quantities, each of 15 mL, of *methylene chloride R*. To the combined lower layers add *anhydrous sodium sulfate R*, shake, filter, and evaporate the filtrate by suitable means at a temperature not exceeding 30 °C. Take up the residue with *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *alverine impurity D CRS* (impurity D citrate) in 5 mL of *water R*, add 1 mL of *concentrated ammonia R* and shake with 3 quantities, each of 5 mL, of *methylene chloride R*. To the combined lower layers add *anhydrous sodium sulfate R*, shake, filter, and evaporate the filtrate by suitable means at a temperature not exceeding 30 °C. Take up the residue with *methylene chloride R*, add 0.2 mL of the test solution and dilute to 2.0 mL with *methylene chloride R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 20.0 mL with *methylene chloride R*.

Reference solution (c) Dissolve 20 mg of *alverine impurity C CRS* in *methylene chloride R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *methylene chloride R*.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.45 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.2 mL/min.

Split ratio 1:11.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Column	0 - 7	120
	7 - 13	120 → 240
	13 - 21	240
	21 - 24	240 → 290
	24 - 39	290
Injection port		290
Detector		290

Detection Flame ionisation.

Injection 1 µL.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to alverine (retention time = about 18 min): impurity C = about 0.5; impurity D = about 0.97.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity D and alverine.

Limits:

— *impurities C, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 80 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.375 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 47.36 mg of $C_{26}H_{35}NO_7$.

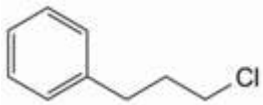
STORAGE

Protected from light.

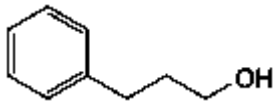
IMPURITIES

Specified impurities *C, D.*

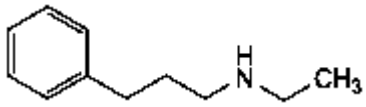
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, E.*



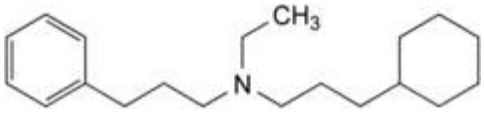
A. 1-chloro-3-phenylpropane,



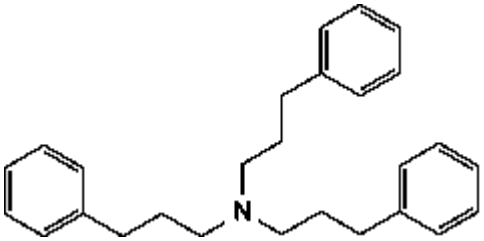
B. 3-phenylpropan-1-ol,



C. *N*-ethyl-3-phenylpropan-1-amine,



D. *N*-(3-cyclohexylpropyl)-*N*-ethyl-3-phenylpropan-1-amine,



www.webofpharma.com

https://thuvienthuocngocanh.com/

E. 3-phenyl-*N*,*N*-bis(3-phenylpropyl)propan-1-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amantadine Capsules

General Notices

Action and use

Viral replication inhibitor (influenza A); dopamine receptor agonist; treatment of influenza and Parkinson's disease.

DEFINITION

Amantadine Capsules contain Amantadine Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of amantadine hydrochloride, $C_{10}H_{17}N,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.2 g of Amantadine Hydrochloride in 10 mL of 0.1M *hydrochloric acid* on a water bath and filter. Add 1 mL of 5M *sodium hydroxide* to the filtrate and extract with 5 mL of *dichloromethane*. Filter the lower layer through *anhydrous sodium sulfate*, wash the sodium sulfate with 2 mL of *dichloromethane* and evaporate the solution to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of amantadine *(RS 006)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.
(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. Prepare a 0.6% w/v solution of *naphthalene* (internal standard) in *toluene* (solution A).

(1) After 45 minutes withdraw a sample of the medium and filter. Transfer 3 mL to a centrifuge tube. Add 1 mL of 5M *sodium hydroxide* and 2 mL of solution A. Shake the tube for approximately 10 minutes and allow the layers to separate. Use the top layer for injection.
(2) To 3 mL of a 0.011% w/v solution of *amantadine hydrochloride BPCRS* in the medium, add 1 mL of 5M *sodium hydroxide* and 2 mL of solution A. Shake the flask for approximately 10 minutes and allow the layers to separate. Use the top layer for injection.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.25 mm) bonded with a 0.25-µm layer of *methylpolysiloxane* (Agilent DB-1 is suitable).

(b) Use *helium* as the carrier gas at 1 mL per minute.

(c) Use the gradient conditions described below.

(d) Use an inlet temperature of 180°.

(e) Use a flame ionisation detector at a temperature of 250°.

(f) Inject 1 µL of each solution

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature	Comment
0-16	100°→200°	linear gradient
16-20	200°	isothermal

DETERMINATION OF CONTENT

Calculate the total content of amantadine hydrochloride, $C_{10}H_{17}N,HCl$, in the medium using the ratios of the area of the peak corresponding to amantadine to the area of the peak due to the internal standard in the chromatograms obtained with solutions (1) and (2), and using the declared content of $C_{10}H_{17}N,HCl$ in *amantadine hydrochloride BPCRS*.

LIMITS

The amount of amantadine hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *gas chromatography*, Appendix III B using the following solutions.

(1) Dissolve a quantity of the contents of the capsules containing 0.1 g of Amantadine Hydrochloride in 2 mL of *water*, add 2 mL of a 20% w/v solution of *sodium hydroxide* and 10 mL of *toluene* and shake for 10 minutes. Separate the upper layer, dry over *anhydrous sodium sulfate* and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with *toluene*. Further dilute 1 volume to 10 volumes with *toluene*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

When the chromatograms are recorded under the prescribed conditions, the retention time of amantadine is about 7 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.2% by *normalisation*;

the sum of the areas of any *secondary peaks* is not greater than 1.0% by *normalisation*.

Disregard any peak with an area less than 0.1% by *normalisation*.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Weigh the contents of 20 capsules. Mix, and powder if necessary. Carry out the method for *gas chromatography*, Appendix III B. Prepare a 0.6% w/v solution of *naphthalene* (internal standard) in *toluene* (solution A).

(1) Dissolve a quantity of the contents of the capsules containing 0.1 g of Amantadine Hydrochloride in 2 mL of *water*, add 2 mL of a 20% w/v solution of *sodium hydroxide* and 10 mL of solution A and shake for 10 minutes. Separate the upper layer, dry over *anhydrous sodium sulfate* and filter.

(2) Prepare the solution in the same manner as for solution (1) but using 0.1 g of *amantadine hydrochloride BPCRS* in 10 mL of *water* in place of the preparation being examined.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{17}N,HCl$ in the capsules using the ratios of the area of the peak corresponding to amantadine to the area of the peak due to the internal standard in the chromatograms obtained with solutions (1) and (2), and using the declared content of $C_{10}H_{17}N,HCl$ in *amantadine hydrochloride BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

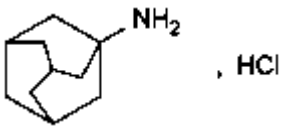
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amantadine Hydrochloride

General Notices

(Ph. Eur. monograph 0463)



$C_{10}H_{18}ClN$ 187.7 *665-66-7*

Action and use

Viral replication inhibitor (influenza A); dopamine receptor agonist; treatment of influenza and Parkinson's disease.

Preparations

Amantadine Capsules

Amantadine Oral Solution

Ph Eur

DEFINITION

Tricyclo[3.3.1.1^{3,7}]decan-1-amine hydrochloride.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

It sublimes on heating.

IDENTIFICATION

https://thuocngocanh.com/

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *amantadine hydrochloride CRS*.

B. To 0.1 g add 1 mL of *pyridine R*, mix and add 0.1 mL of *acetic anhydride R*. Heat to boiling for about 10 s. Pour the hot solution into 10 mL of *dilute hydrochloric acid R*, cool to 5 °C and filter. The precipitate, washed with *water R* and dried *in vacuo* at 60 °C for 1 h, melts (2.2.14) at 147 °C to 151 °C.

C. Dissolve 0.2 g in 1 mL of *0.1 M hydrochloric acid*. Add 1 mL of a 500 g/L solution of *sodium nitrite R*. A white precipitate is formed.

D. 1 mL of solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Acidity or alkalinity

Dilute 2 mL of solution S to 10 mL with *carbon dioxide-free water R*. Add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Related substances

Gas chromatography (2.2.28).

Internal standard solution Dissolve 0.500 g of *adamantane R* in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

Test solution Weigh 0.5 g of the substance to be examined into a centrifuge tube. Add 9 mL of *methylene chloride R* and 10 mL of a 210 g/L solution of *sodium hydroxide R*. Shake for 10 min. Discard the upper layer. Dry the lower layer over *anhydrous sodium sulfate R*. Filter and collect the filtrate in a volumetric flask. Add 0.1 mL of the internal standard solution and dilute to 10.0 mL with *methylene chloride R*.

Reference solution Weigh 5 mg of *amantadine hydrochloride CRS* into a centrifuge tube. Add 9 mL of *methylene chloride R* and 10 mL of a 210 g/L solution of *sodium hydroxide R*. Shake for 10 min. Discard the upper layer. Dry the lower layer over *anhydrous sodium sulfate R*. Filter and collect the filtrate in a volumetric flask. Add 1.0 mL of the internal standard solution and dilute to 100.0 mL with *methylene chloride R*.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *base-deactivated phenyl(5)methyl(95)polysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 4 mL/min.

Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	70
	5 - 23	70 → 250
	23 - 40	250
Injection port		220
Detector		300

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to amantadine (retention time = about 14 min): internal standard = about 0.8.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to the internal standard and amantadine.

Limits:

— *unspecified impurities*: calculate the ratio (R_1) of the area of the peak due to amantadine to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the area of any peak, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than R_1 (0.10 per cent);

— *total*: calculate the ratio (R_2) of 3 times the area of the peak due to amantadine to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than R_2 (0.3 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: calculate the ratio (R_3) of 0.5 times the area of the peak due to amantadine to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the area of any peak, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: disregard any peak with a ratio less than R_3 (0.05 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 2.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

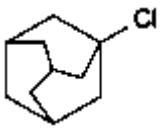
ASSAY

Dissolve 0.150 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

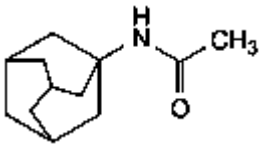
1 mL of *0.1 M sodium hydroxide* is equivalent to 18.77 mg of $C_{10}H_{18}ClN$.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



A. 1-chlorotricyclo[3.3.1.1^{3,7}]decane,



B. *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)acetamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amantadine Oral Solution

General Notices

Action and use

Viral replication inhibitor (influenza A); dopamine receptor agonist; treatment of influenza and Parkinson's disease.

DEFINITION

Amantadine Oral Solution is a solution of Amantadine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of amantadine hydrochloride, $C_{10}H_{17}N,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Acidify a volume of the oral solution containing 0.1 g of Amantadine Hydrochloride with 1M *hydrochloric acid* and extract with three 15-mL quantities of *ether*. Discard the upper layer, add 2M *sodium hydroxide* to the retained lower layer until it is just alkaline and extract with two 10-mL quantities of *dichloromethane*. Filter the combined lower layers through *anhydrous sodium sulfate* and evaporate the filtrate to dryness under reduced pressure. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of amantadine *(RS 006)*.

TESTS

Related substances

Carry out the method for *gas chromatography*, Appendix III B using the following solutions.

(1) Mix, with swirling, a volume of the oral solution containing 0.1 g of Amantadine Hydrochloride with 4 mL of a 20% w/v solution of *sodium hydroxide*, add 10 mL of *toluene*, shake the mixture for 10 minutes, allow the layers to separate and use the upper layer.

(2) Dilute 1 volume of solution (1) to 100 volumes with *toluene*. Further dilute 1 volume to 10 volumes with *toluene*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.25 mm) bonded with a 0.25-µm layer of *methylpolysiloxane* (Agilent DB-1 is suitable).

(b) Use *helium* as the carrier gas at 1 mL per minute.

(c) Use the gradient conditions described below.

(d) Use an inlet temperature of 180°.

(e) Use a flame ionisation detector at a temperature of 250°.

(f) Inject 1 µL of each solution

www.webofpharma.com

https://thuocngocanh.com/

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature	Comment
0-16	100°→200°	linear gradient
16-20	200°	isothermal

When the chromatograms are recorded under the prescribed conditions, the retention time of amantadine is about 7 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.2% by *normalisation*;

the sum of the areas of any *secondary peaks* is not greater than 1.0% by *normalisation*.

Disregard any peak with an area less than 0.1% by *normalisation*.

ASSAY

Carry out the method for *gas chromatography*, Appendix III B. Prepare a 0.6% w/v solution of *naphthalene* (internal standard) in *toluene* (solution A).

(1) Mix, with swirling, a weighed quantity of the oral solution containing 0.1 g of Amantadine Hydrochloride with 4 mL of a 20% w/v solution of *sodium hydroxide* and add 10 mL of solution A. Shake the mixture for 10 minutes, allow the layers to separate and use the upper layer.
(2) Prepare the solution in the same manner as solution (1) using 0.1 g of *amantadine hydrochloride BPCRS* in 10 mL of water in place of the preparation being examined.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{17}N$,HCl in the oral solution using the ratios of the area of the peak corresponding to amantadine to the area of the peak due to the internal standard in the chromatograms obtained with solutions (1) and (2) and using the declared content of $C_{10}H_{17}N$,HCl in *amantadine hydrochloride BPCRS*.

STORAGE

Amantadine Oral Solution should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

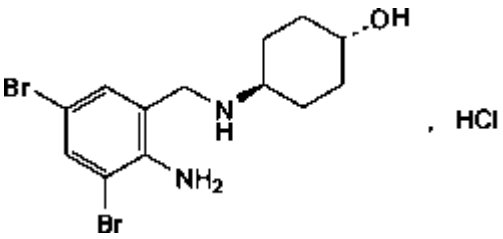
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ambroxol Hydrochloride

General Notices

(Ph. Eur. monograph 1489)



$C_{13}H_{19}Br_2ClN_2O$ 414.6 *23828-92-4*

Action and use

Mucolytic expectorant.

Ph Eur

DEFINITION

trans-4-[(2-Amino-3,5-dibromobenzyl)amino]cyclohexanol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Sparingly soluble in water, soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20.0 mg in *dilute sulfuric acid R1* and dilute to 100.0 mL with the same acid. Dilute 2.0 mL of the solution to 10.0 mL with *dilute sulfuric acid R1*.

Spectral range 200-350 nm.

Absorption maxima At 245 nm and 310 nm.

Absorbance ratio A_{245}/A_{310} = 3.2 to 3.4.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *ambroxol hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 50 mg of *ambroxol hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *propanol R*, *ethyl acetate R*, *hexane R* (1:10:20:70 *V/V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 25 mg in 2.5 mL of *water R*, mix with 1.0 mL of *dilute ammonia R1* and allow to stand for 5 min. Filter and acidify the filtrate with *dilute nitric acid R*. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.75 g in *methanol R* and dilute to 15 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

www.webofpharma.com

https://thuocngocanh.com/

pH (*2.2.3*)

4.5 to 6.0.

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) In order to prepare impurity B *in situ*, dissolve 5 mg of the substance to be examined in 0.2 mL of *methanol R*, add 0.04 mL of a mixture of 1 volume of *formaldehyde solution R* and 99 volumes of *water R*. Heat at 60 °C for 5 min. Evaporate to dryness under a current of nitrogen. Dissolve the residue in 5 mL of *water R* and dilute to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase A mixture of equal volumes of *acetonitrile R* and a solution prepared as follows: dissolve 1.32 g of *ammonium phosphate R* in 900 mL of *water R*, adjust to pH 7.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 248 nm.

Injection 20 µL.

Run time 3 times the retention time of ambroxol.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to ambroxol (retention time = about 9 min): impurity B = about 0.6.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurity B and ambroxol.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent),

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 70 mL of *ethanol (96 per cent) R* and add 5 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

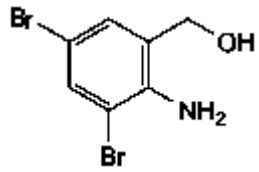
1 mL of *0.1 M sodium hydroxide* is equivalent to 41.46 mg of $C_{13}H_{19}Br_2ClN_2O$.

STORAGE

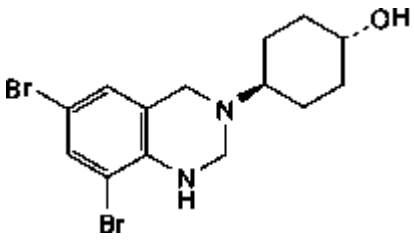
Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E.



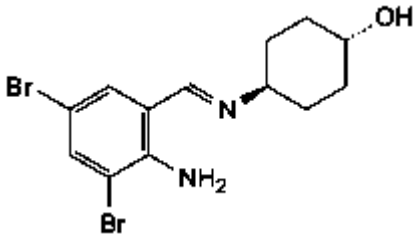
A. (2-amino-3,5-dibromophenyl)methanol,



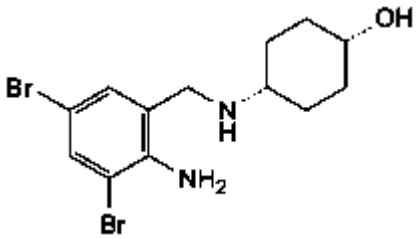
B. *trans*-4-(6,8-dibromo-1,4-dihydroquinazolin-3(2*H*)-yl)cyclohexanol,

www.webofpharma.com

https://thuocngocanh.com/



C. *trans*-4-[[(*E*)-2-amino-3,5-dibromobenzyliden]amino]cyclohexanol,



D. *cis*-4-[(2-amino-3,5-dibromobenzyl)amino]cyclohexanol,

E. 2-amino-3,5-dibromobenzaldehyde.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

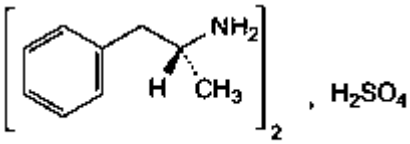
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amfetamine Sulfate

General Notices

Amfetamine Sulphate

(Ph. Eur. monograph 0368)



and enantiomer

$C_{18}H_{28}N_2O_4S$ 368.5 *60-13-9*

Action and use

Releases dopamine; central nervous system stimulant.

Ph Eur

DEFINITION

Bis[(2*RS*)-1-phenylpropan-2-amine] sulfate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, B, D.

Second identification: C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *amfetamine sulfate CRS*.

C. To 50 mL of solution S add 5 mL of *strong sodium hydroxide solution R* and 0.5 mL of *benzoyl chloride R* and shake. Continue to add *benzoyl chloride R* in portions of 0.5 mL, shaking after each addition, until no further precipitate is formed. Filter, wash the precipitate with *water R*, recrystallise twice from a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*, then dry at 100-105 °C. The crystals melt (2.2.14) at 131 °C to 135 °C.

D. Solution S (see Tests) gives reaction (a) of sulfates (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Optical rotation (2.2.7)

-0.04° to + 0.04° (measured in a 2 dm tube), determined on solution S.

Acidity or alkalinity

To 25 mL of solution S add 0.1 mL of *methyl red solution R*. Not more than 0.1 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Solvent mixture Mix 5 mL of *trifluoroacetic acid R* and 900 mL of *water for chromatography R*, adjust to pH 2.2 with *concentrated ammonia R* and dilute to 1000 mL with *acetonitrile R*.

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *1-phenylpropan-2-ol R* (impurity A) and 5 mg of *benzaldehyde R* (impurity D) in the solvent mixture and dilute to 10 mL with the solvent mixture. Dilute 1 mL of the solution to 100 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: solvent mixture;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	100	0
1 - 16	100 → 65	0 → 35
16 - 21	65 → 0	35 → 100
21 - 23	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 257 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and D.

Relative retention With reference to amfetamine (retention time = about 8 min): impurity D = about 1.6; impurity A = about 1.7.

System suitability Reference solution (b):

— resolution: minimum 4.0 between the peaks due to impurities D and A.

Calculation of percentage contents:

— for each impurity, use the concentration of amfetamine sulfate in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

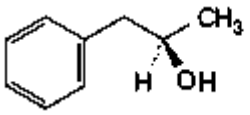
1 mL of *0.1 M perchloric acid* is equivalent to 36.85 mg of $C_{18}H_{28}N_2O_4S$.

STORAGE

Protected from light.

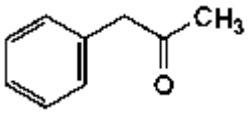
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.

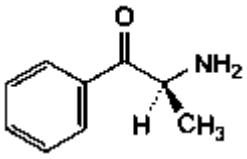


and enantiomer

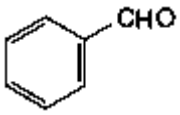
A. (2*RS*)-1-phenylpropan-2-ol,



B. 1-phenylpropan-2-one,



C. (2*S*)-2-amino-1-phenylpropan-1-one (cathinone),



D. benzaldehyde.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

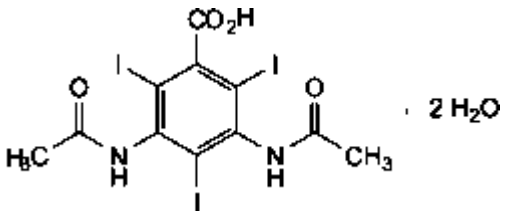
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amidotrizoic Acid Dihydrate

General Notices

(Ph. Eur. monograph 0873)



$C_{11}H_9I_3N_2O_4,2H_2O$ 650 *50978-11-5*

Action and use

Iodinated contrast medium.

Preparation

Meglumine Amidotrizoate Injection

Ph Eur

DEFINITION

3,5-Bis(acetylamino)-2,4,6-triiodobenzoic acid dihydrate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water and in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *amidotrizoic acid dihydrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in a 3 per cent *V/V* solution of *ammonia R* in *methanol R* and dilute to 5 mL with the same solution.

Reference solution Dissolve 25 mg of *amidotrizoic acid dihydrate CRS* in a 3 per cent *V/V* solution of *ammonia R* in *methanol R* and dilute to 5 mL with the same solution.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *methyl ethyl ketone R*, *toluene R* (20:25:60 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air until the solvents have evaporated.

Detection In ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Heat 50 mg gently in a small porcelain dish over a naked flame. Violet vapour is evolved.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 1.0 g in *dilute sodium hydroxide solution R* and dilute to 20 mL with the same solution.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Dissolve 0.250 g of *sodium hydroxide R* and 0.860 g of *sodium dihydrogen phosphate R* in 50 mL of *water R* and dilute to 1000 mL with the same solvent.

Test solution Dissolve 40.0 mg of the substance to be examined in 10.0 mL of the solvent mixture with the aid of ultrasound.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *amidotrizoic acid for system suitability CRS* (impurities A, B, C and D) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 3.4 g of *tetrabutylammonium hydrogen sulfate R* in a mixture of 230 mL of *acetonitrile R* and 770 mL of *water R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 236 nm.

Injection 20 µL.

Run time 4 times the retention time of amidotrizoic acid.

Identification of impurities Use the chromatogram supplied with *amidotrizoic acid for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to amidotrizoic acid (retention time = about 5 min): impurity B = about 0.8; impurity C = about 0.9; impurity A = about 1.4; impurity D = about 1.8.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities B and C in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 25 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurities A, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent), except for the peaks due to impurities A and D.

Halides expressed as chlorides (2.4.4)

Maximum 150 ppm.

Dissolve 0.55 g in a mixture of 4 mL of *dilute sodium hydroxide solution R* and 15 mL of *water R*. Add 6 mL of *dilute nitric acid R* and filter.

Free aromatic amines

Maintain the solutions and reagents in iced water, protected from bright light To 0.50 g in a 50 mL volumetric flask add 15 mL of *water R*. Shake and add 1 mL of *dilute sodium hydroxide solution R*. Cool in iced water, add 5 mL of a freshly prepared 5 g/L solution of *sodium nitrite R* and 12 mL of *dilute hydrochloric acid R*. Shake gently and allow to stand for exactly 2 min after adding the hydrochloric acid. Add 10 mL of a 20 g/L solution of *ammonium sulfamate R*. Allow to stand for 5 min, shaking frequently, and add 0.15 mL of a 100 g/L solution of *α-naphthol R* in *ethanol (96 per cent) R*. Shake and allow to stand for 5 min. Add 3.5 mL of *buffer solution pH 10.9 R*, mix and dilute to 50.0 mL with *water R*. The absorbance (2.2.25), measured within 20 min at 485 nm using as the compensation liquid a solution prepared at the same time and in the same manner but omitting the substance to be examined, is not greater than 0.30.

Loss on drying (2.2.32)

4.5 per cent to 7.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.150 g in a 250 mL round-bottomed flask add 5 mL of *strong sodium hydroxide solution R*, 20 mL of *water R*, 1 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 30 min. Allow to cool and rinse the condenser with 20 mL of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (2.1.2) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 40 mL of *dilute sulfuric acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (2.2.20).

1 mL of *0.1 M silver nitrate* is equivalent to 20.47 mg of $C_{11}H_9I_3N_2O_4$.

STORAGE

Protected from light.

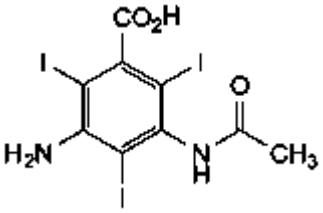
IMPURITIES

Specified impurities *A, B, D.*

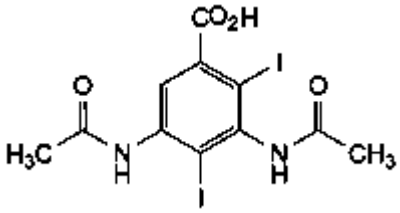
www.webofpharma.com

https://thuocngocanh.com/

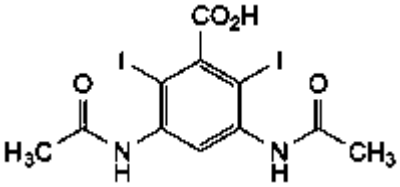
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, E.



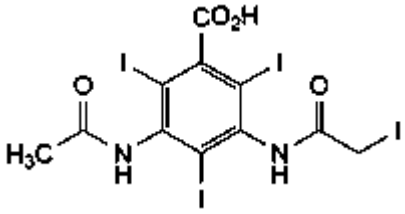
A. 3-(acetylamino)-5-amino-2,4,6-triiodobenzoic acid,



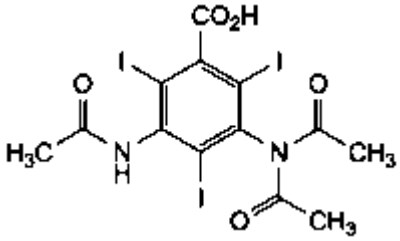
B. 3,5-bis(acetylamino)-2,4-diiodobenzoic acid,



C. 3,5-bis(acetylamino)-2,6-diiodobenzoic acid,



D. 3-(acetylamino)-5-[(iodoacetyl)amino]-2,4,6-triiodobenzoic acid,



E. 3-(acetylamino)-5-(diacetylamino)-2,4,6-triiodobenzoic acid.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

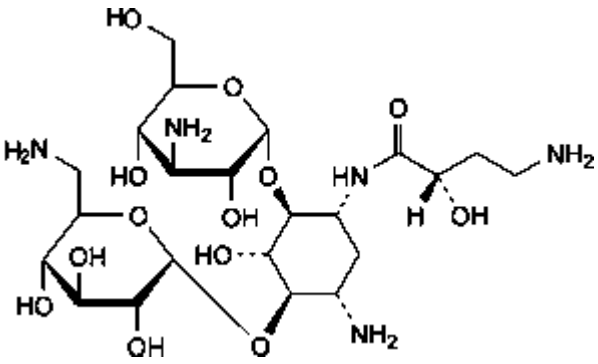
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amikacin

General Notices

(Ph. Eur. monograph 1289)



$C_{22}H_{43}N_5O_{13}$ 585.6 *37517-28-5*

Action and use

Aminoglycoside antibacterial.

Ph Eur

DEFINITION

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine.

Antimicrobial substance obtained from kanamycin A.

Semi-synthetic product derived from a fermentation product.

Content

96.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Sparingly soluble in water, slightly soluble in methanol, practically insoluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *amikacin CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *amikacin CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *kanamycin monosulfate CRS* in 1 mL of the test solution and dilute to 10 mL with *water R*.

Plate *TLC silica gel plate R*.

Mobile phase *methylene chloride R*, *ammonia R*, *methanol R* (25:30:40 *V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R1* and heat at 110 °C for 5 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

pH (*2.2.3*)

9.5 to 11.5.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 97 to + 105 (anhydrous substance).

Dissolve 0.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of *amikacin for system suitability CRS* (containing impurities A, B, F and H) in mobile phase A and dilute to 10 mL with mobile phase A.

Reference solution (d) Dissolve 5.0 mg of *amikacin impurity I CRS* in mobile phase A and dilute to 20.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: a mixture prepared with *carbon dioxide-free water R*, containing 1.8 g/L of *sodium octanesulfonate R*, 20 g/L of *anhydrous sodium sulfate R1*, 1.4 per cent *V/V* of *tetrahydrofuran R*, and 5 per cent *V/V* of *0.2 M potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*; degas;

— *mobile phase B*: a mixture prepared with *carbon dioxide-free water R*, containing 1.8 g/L of *sodium octanesulfonate R*, 28 g/L of *anhydrous sodium sulfate R1*, 1.4 per cent *V/V* of *tetrahydrofuran R*, and 5 per cent *V/V* of *0.2 M potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*; degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 38.0	100 → 30	0 → 70
38.0 - 38.1	30 → 0	70 → 100
38.1 - 68	0	100

Flow rate 1.0 mL/min.

Post-column solution Mixture of 1 volume of *carbonate-free sodium hydroxide solution R* and 24 volumes of previously degassed *carbon dioxide-free water R*, which is added in a pulseless manner to the column effluent using a 375 µL polymeric mixing coil.

Flow rate of post-column solution 0.3 mL/min.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Detection Pulsed amperometric detector or equivalent with a gold indicator electrode, a silver-silver chloride reference electrode, and a stainless steel auxiliary electrode which is the cell body, held at respectively + 0.05 V detection, + 0.75 V oxidation and - 0.15 V reduction potentials, with pulse durations according to the instrument used.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *amikacin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, F and H; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity I.

Relative retention With reference to amikacin (retention time = about 28 min): impurity I = about 0.13; impurity F = about 0.92; impurity B = about 0.95; impurity A = about 1.62; impurity H = about 1.95.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to amikacin; if necessary, adjust the volume of tetrahydrofuran in the mobile phase.

Calculation of percentage contents:

— for impurity I, use the concentration of impurity I in reference solution (d);

— for impurities other than I, use the concentration of amikacin in reference solution (a).

Limits:

— *impurities A, B, F, H, I*: for each impurity, maximum 0.5 per cent;

— *any other impurity*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.1 per cent.

Water (2.5.12)

Maximum 8.5 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution Dissolve 50.0 mg of *amikacin CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase A mixture prepared with *carbon dioxide-free water R*, containing 1.8 g/L of *sodium octanesulfonate R*, 20 g/L of *anhydrous sodium sulfate R1*, 5.8 per cent *V/V* of *acetonitrile R1*, and 5 per cent *V/V* of *0.2 M potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*; degas.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 20 µL.

Run time 1.3 times the retention time of amikacin.

Retention time Amikacin = about 30 min.

System suitability Reference solution:

— *symmetry factor*: maximum 1.5 for the peak due to amikacin; if necessary, adjust the amount of *acetonitrile R1* in the mobile phase; peak splitting may be observed when the retention time becomes too short;

— *repeatability*: maximum relative standard deviation of 1.5 per cent after 6 injections.

Calculate the percentage content of $C_{22}H_{43}N_5O_{13}$ taking into account the assigned content of *amikacin CRS*.

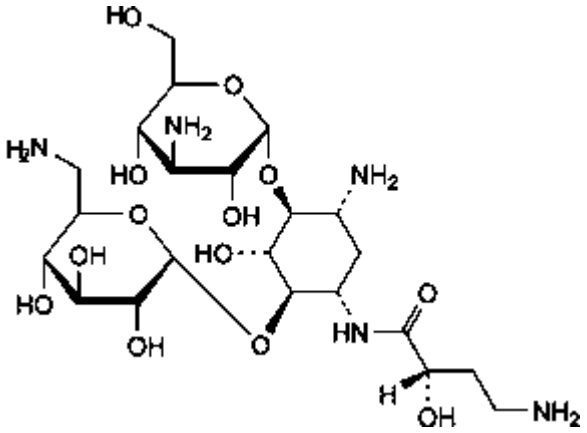
IMPURITIES

Specified impurities *A, B, F, H, I.*

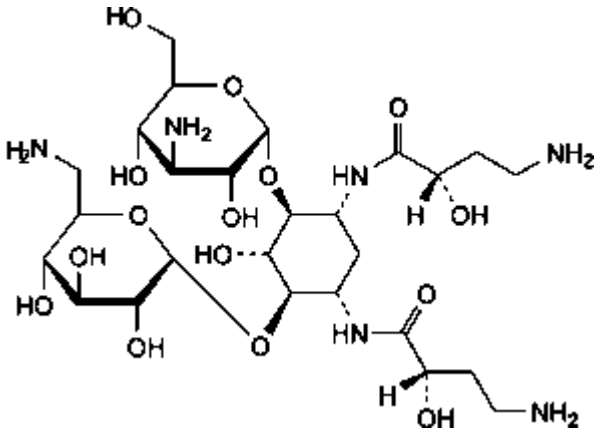
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, G.*

www.webofpharma.com

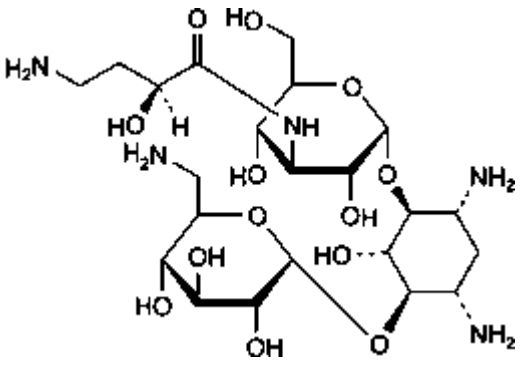
https://thuocngocanh.com/



A. 4-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-6-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-L-streptamine,



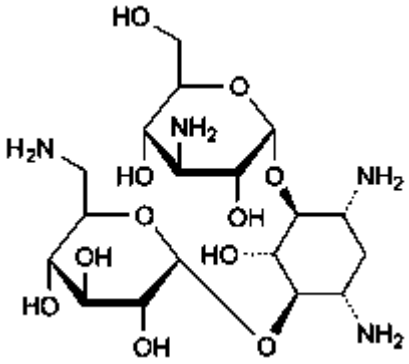
B. 4-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-6-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-1,3-*N*-bis[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-L-streptamine,



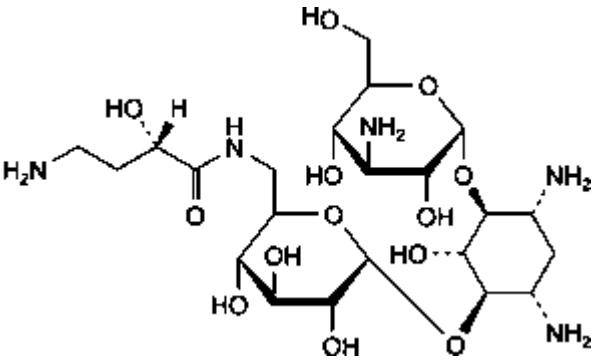
C. 4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-6-*O*-[3-[[(2*S*)-4-amino-2-hydroxybutanoyl]amino]-3-deoxy-α-D-glucopyranosyl]-2-deoxy-D-streptamine,

www.webofpharma.com

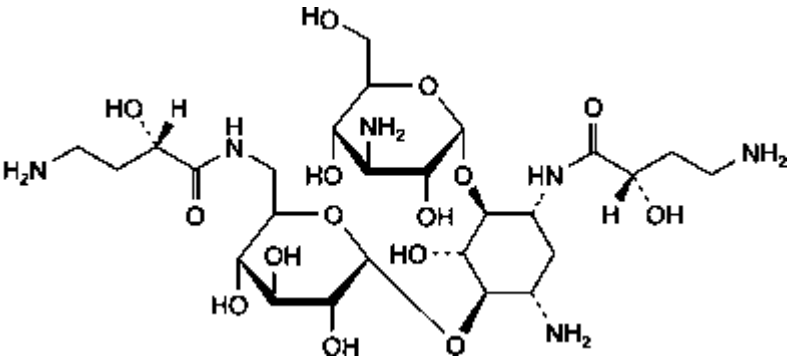
https://thuocngocanh.com/



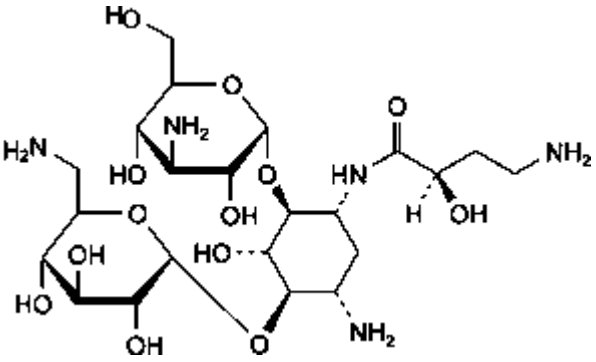
D. 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxy-D-streptamine (kanamycin),



E. 4-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-6-*O*-[6-[[(2*S*)-4-amino-2-hydroxybutanoyl]amino]-6-deoxy-α-D-glucopyranosyl]-2-deoxy-L-streptamine,



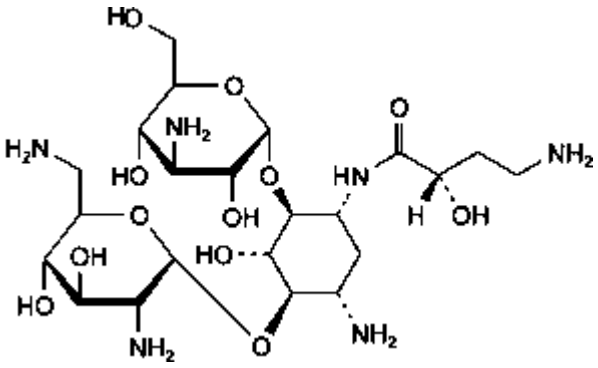
F. 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-[6-[(2*S*)-4-amino-2-hydroxybutanoyl]amino-6-deoxy-α-D-glucopyranosyl]-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine,



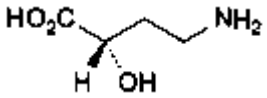
www.webofpharma.com

https://thuocngocanh.com/

G. 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-[(2*R*)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine,



H. 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-2-deoxy-D-streptamine,



I. (2*S*)-4-amino-2-hydroxybutanoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amikacin Injection

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Amikacin Injection is a sterile solution of Amikacin Sulfate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of amikacin, $C_{22}H_{43}N_5O_{13}$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

In the test for Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

Acidity

pH, 3.5 to 5.5, Appendix V L.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a volume of the injection, if necessary, to produce a solution containing the equivalent of 1.0% w/v of amikacin.
(2) 0.013% w/v of *amikacin sulfate BPCRS*.
(3) 1.0% w/v of *amikacin for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.
(5) *Water* (blank solution).

Derivatise the solutions prior to analysis using the following method.

Transfer 0.2 mL of the solution being examined to a ground glass stoppered vial. Add 2 mL of a 1.0% w/v solution of *2,4,6-trinitrobenzenesulfonic acid*. To this solution add 3 mL of *pyridine* and close the vial tightly. Shake vigorously for 30 seconds and heat on a

www.webofpharma.com

https://thuocngocanh.com/

water bath at 75° for 2 hours. Cool in cold water for 2 minutes and add 2 mL of *glacial acetic acid*. Shake vigorously for 30 seconds. Store the derivatised solutions at 10° prior to and during analysis.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 340 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 4 times the retention time of amikacin.

MOBILE PHASE

30 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 6.5 with a 2.2% w/v solution of *potassium hydroxide*, and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the relative retention of amikacin impurity A with reference to that of amikacin (retention time, about 12 minutes), is about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to amikacin and impurity A is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the sum of the areas of all secondary peaks is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peaks corresponding to the peaks in the chromatogram obtained with solution (5), any peak eluting before the principal peak, and any peak with an area of less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, with *water BET* to give a solution containing the equivalent of 10 mg per mL of amikacin (solution A). The endotoxin limit concentration of solution A is 3.3 IU of endotoxin per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dilute a volume of the injection containing the equivalent of 37 mg of amikacin to 10 mL.

(2) 0.50% w/v of *amikacin sulfate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Supelco Discovery C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 200 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.18% w/v of *sodium octanesulfonate* and 2.00% w/v *sodium sulfate* in a mixture of 68 volumes of *acetonitrile R1*, 40 volumes of 0.2M potassium dihydrogen phosphate adjusted to pH 3.0 with *dilute phosphoric acid*, and 936 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{43}N_5O_{13}$ in the injection using the declared content of $C_{22}H_{43}N_5O_{13},2H_2SO_4$ in *amikacin sulfate BPCRS*. Each mg of $C_{22}H_{43}N_5O_{13},2H_2SO_4$ is equivalent to 0.7488 mg of $C_{22}H_{43}N_5O_{13}$.

LABELLING

The strength is stated in terms of the equivalent amount of amikacin in a suitable dose-volume.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Amikacin Sulfate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

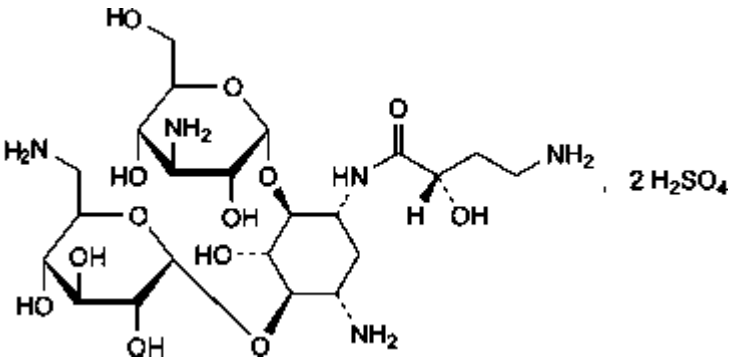
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amikacin Sulfate

General Notices

Amikacin Sulphate

(Ph. Eur. monograph 1290)



$C_{22}H_{47}N_5O_{21}S_2$ 782 *39831-55-5*

Action and use

Aminoglycoside antibacterial.

Preparation

Amikacin Injection

Ph Eur

DEFINITION

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine sulfate.

Antimicrobial substance obtained from kanamycin A.

Semi-synthetic product derived from a fermentation product.

Content

96.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

https://thuocngocanh.com/

White or almost white powder.

Solubility

Freely soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *amikacin sulfate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *amikacin sulfate CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *kanamycin monosulfate CRS* in 1 mL of the test solution and dilute to 10 mL with *water R*.

Plate *TLC silica gel plate R*.

Mobile phase *methylene chloride R*, *ammonia R*, *methanol R* (25:30:40 *V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R1* and heat at 110 °C for 5 min.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. It gives reaction (a) of sulfates (2.3.1).

TESTS

pH (2.2.3)

2.0 to 4.0.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

www.webofpharma.com

https://thuocngocanh.com/

+ 76 to + 84 (dried substance).

Dissolve 0.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 33 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of *amikacin for system suitability CRS* (containing impurities A, B, F and H) in mobile phase A and dilute to 10 mL with mobile phase A.

Reference solution (d) Dissolve 6.6 mg of *amikacin impurity I CRS* in mobile phase A and dilute to 20.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: a mixture prepared with *carbon dioxide-free water R*, containing 1.8 g/L of *sodium octanesulfonate R*, 20 g/L of *anhydrous sodium sulfate R1*, 1.4 per cent *V/V* of *tetrahydrofuran R*, and 5 per cent *V/V* of *0.2 M potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*; degas;

— *mobile phase B*: a mixture prepared with *carbon dioxide-free water R*, containing 1.8 g/L of *sodium octanesulfonate R*, 28 g/L of *anhydrous sodium sulfate R1*, 1.4 per cent *V/V* of *tetrahydrofuran R*, and 5 per cent *V/V* of *0.2 M potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*; degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 38.0	100 → 30	0 → 70
38.0 - 38.1	30 → 0	70 → 100
38.1 - 68	0	100

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Post-column solution Mixture of 1 volume of *carbonate-free sodium hydroxide solution R* and 24 volumes of previously degassed *carbon dioxide-free water R*, which is added in a pulseless manner to the column effluent using a 375 µL polymeric mixing coil.

Flow rate of post-column solution 0.3 mL/min.

Detection Pulsed amperometric detector or equivalent with a gold indicator electrode, a silver-silver chloride reference electrode, and a stainless steel auxiliary electrode which is the cell body, held at respectively + 0.05 V detection, + 0.75 V oxidation and - 0.15 V reduction potentials, with pulse durations according to the instrument used.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *amikacin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, F and H; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity I.

Relative retention With reference to amikacin (retention time = about 28 min): impurity I = about 0.13; impurity F = about 0.92; impurity B = about 0.95; impurity A = about 1.62; impurity H = about 1.95.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to amikacin; if necessary, adjust the volume of tetrahydrofuran in the mobile phase.

Calculation of percentage contents:

— for impurity I, use the concentration of impurity I in reference solution (d);

— for impurities other than I, use the concentration of amikacin sulfate in reference solution (a).

Limits:

— *impurities A, B, F, H, I*: for each impurity, maximum 0.5 per cent;

— *any other impurity*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.1 per cent.

Sulfate

23.3 per cent to 25.8 per cent (dried substance).

Dissolve 0.250 g in 100 mL of *water R* and adjust the solution to pH 11 using *concentrated ammonia R*. Add 10.0 mL of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate* adding 50 mL of *ethanol (96 per cent) R* when the colour

www.webofpharma.com

https://thuocngocanh.com/

of the solution begins to change and continue the titration until the violet-blue colour disappears.

1 mL of *0.1 M barium chloride* is equivalent to 9.606 mg of sulfate (SO_4).

Loss on drying (*2.2.32*)

Maximum 13.0 per cent, determined on 0.500 g by drying in an oven at 105 °C at a pressure not exceeding 0.7 kPa for 3 h.

Pyrogens (*2.6.8*)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of pyrogens, it complies with the test for pyrogens. Inject per kilogram of the rabbit's mass 5 mL of a solution containing 25 mg of the substance to be examined in *water for injections R*.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 37.4 mg of *amikacin CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mixture containing 1.8 g/L of *sodium octanesulfonate R*, 20 g/L of *anhydrous sodium sulfate R1*, 5.8 per cent *V/V* of *acetonitrile R1*, and 5 per cent *V/V* of *0.2 M potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *dilute phosphoric acid R*; degas.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 20 µL.

Run time 1.3 times the retention time of amikacin.

Retention time Amikacin = about 30 min.

System suitability Reference solution:

— *symmetry factor*: maximum 1.5 for the peak due to amikacin; if necessary, adjust the amount of *acetonitrile R1* in the mobile phase; peak splitting may be observed when the retention time becomes too short;

www.webofpharma.com

https://thuocngocanh.com/

— *repeatability*: maximum relative standard deviation of 1.5 per cent after 6 injections.

Calculate the percentage content of $C_{22}H_{47}N_5O_{21}S_2$ taking into account the assigned content of *amikacin CRS* and a correction factor of 1.335.

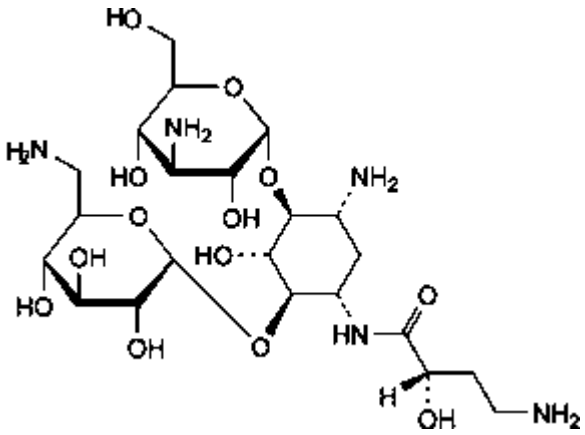
STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

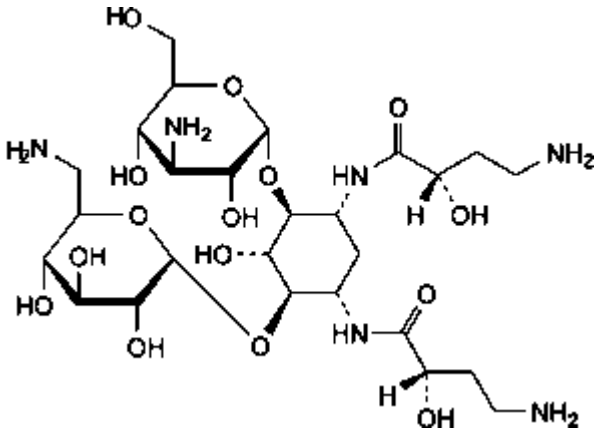
IMPURITIES

Specified impurities *A, B, F, H, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, G.*



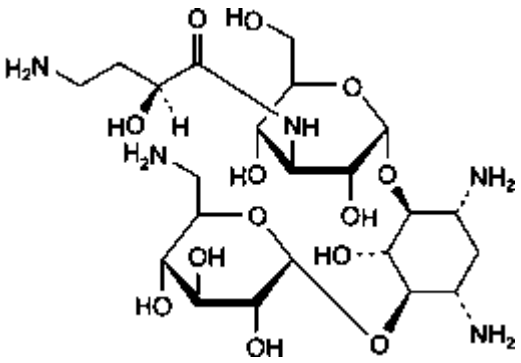
A. 4-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-6-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-L-streptamine,



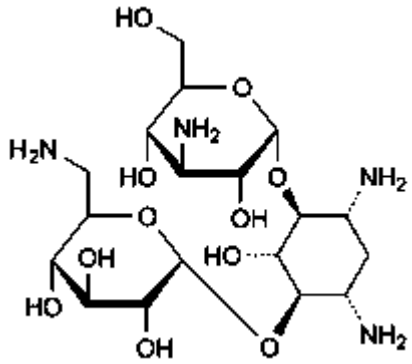
B. 4-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-6-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-1,3-*N*-bis[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-L-streptamine,

www.webofpharma.com

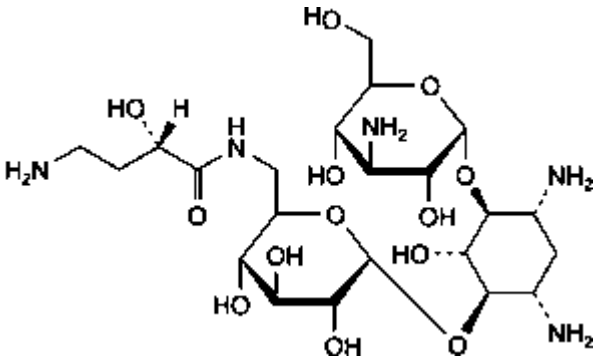
https://thuocngocanh.com/



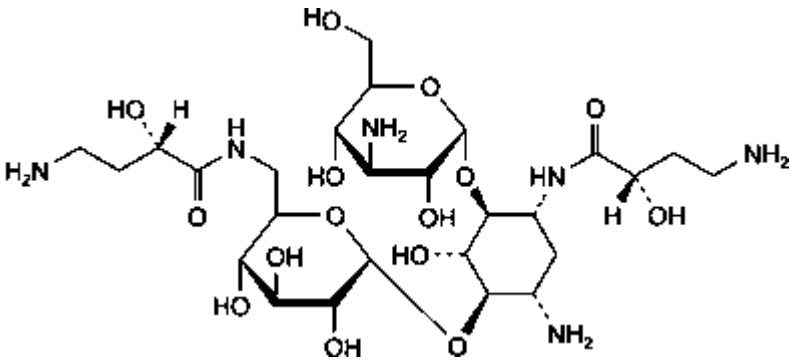
C. 4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-6-*O*-[3-[[(2*S*)-4-amino-2-hydroxybutanoyl]amino]-3-deoxy-α-D-glucopyranosyl]-2-deoxy-D-streptamine,



D. 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxy-D-streptamine (kanamycin),



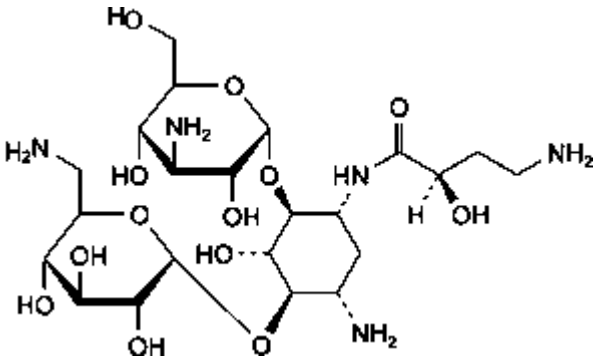
E. 4-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-6-*O*-[6-[[(2*S*)-4-amino-2-hydroxybutanoyl]amino]-6-deoxy-α-D-glucopyranosyl]-2-deoxy-L-streptamine,



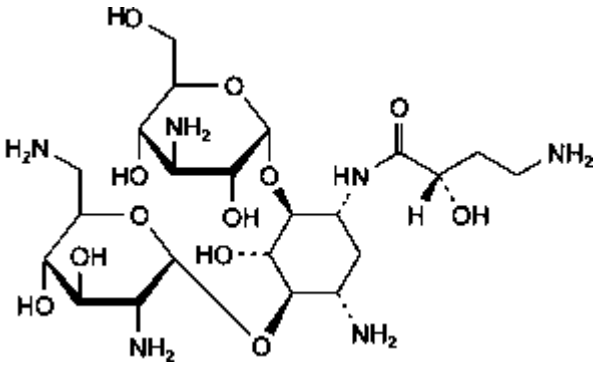
www.webofpharma.com

https://thuocngocanh.com/

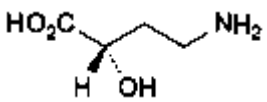
F. 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-[6-[(2*S*)-4-amino-2-hydroxybutanoyl]amino-6-deoxy-α-D-glucopyranosyl]-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine,



G. 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-[(2*R*)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine,



H. 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-2-deoxy-D-streptamine,



I. (2*S*)-4-amino-2-hydroxybutanoic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

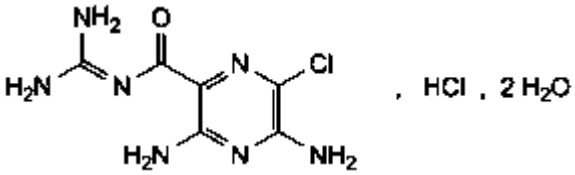
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amiloride Hydrochloride Dihydrate

General Notices

(Ph. Eur. monograph 0651)



$C_6H_9Cl_2N_7O,2H_2O$ 302.1 *17440-83-4*

Action and use

Sodium channel blocker; potassium-sparing diuretic.

Preparations

Amiloride Tablets

Co-amilofruse Tablets

Co-amilozide Oral Solution

Co-amilozide Tablets

Ph Eur

DEFINITION

3,5-Diamino-6-chloro-*N*-(diaminomethylidene)pyrazine-2-carboxamide hydrochloride dihydrate.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Pale yellow or greenish-yellow powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Slightly soluble in water and in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

First identification: A, C, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *amiloride hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 5 mg of *amiloride hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *propanol R* (30:70 *V/V*).

Application 5 µL; the volume may be adapted according to the type of plate used.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent. 2 mL of the solution gives reaction (a) of chlorides (2.3.1); acidify with 0.5 mL of *dilute acetic acid R*, instead of *dilute nitric acid R*.

D. Water (see Tests).

TESTS

Free acid

Dissolve 1.0 g in a mixture of 50 mL of *methanol R* and 50 mL of *water R* and titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). Not more than 0.3 mL of *0.1 M sodium hydroxide* is required to reach the end-point.

Related substances

Liquid chromatography (2.2.29).

www.webofpharma.com

https://thuocngocanh.com/

Solution A Dissolve 2.76 g of *sodium dihydrogen phosphate monohydrate R* in 850 mL of *water for chromatography R*, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of *methanol R* and dilute to 10.0 mL with solution A.

Reference solution (a) Dissolve 2 mg of *amiloride impurity A CRS* in 0.5 mL of *methanol R*, add 0.5 mL of the test solution and dilute to 10 mL with solution A.

Reference solution (b) Dissolve 4 mg of *amiloride for peak identification CRS* (containing impurity C) in 0.5 mL of *methanol R* and dilute to 2 mL with solution A.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Dissolve 0.8 g of *sodium hexanesulfonate monohydrate R* in a mixture of 80 mL of *acetonitrile R1* and 920 mL of solution A.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Run time Twice the retention time of amiloride.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *amiloride for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to amiloride (retention time = about 10 min): impurity C = about 0.5; impurity A = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity A and amiloride.

Calculation of percentage contents:

— for each impurity, use the concentration of amiloride hydrochloride dihydrate in reference solution (c).

Limits:

— *impurity C*: maximum 0.2 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

11.0 per cent to 13.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 26.61 mg of $C_6H_9Cl_2N_7O$.

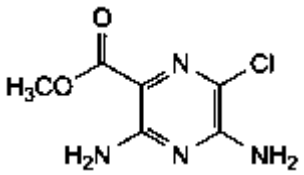
STORAGE

Protected from light.

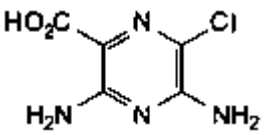
IMPURITIES

Specified impurities C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



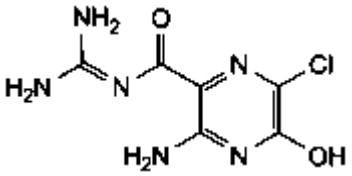
A. methyl 3,5-diamino-6-chloropyrazine-2-carboxylate,



B. 3,5-diamino-6-chloropyrazine-2-carboxylic acid,

www.webofpharma.com

https://thuocngocanh.com/



C. 3-amino-6-chloro-*N*-(diaminomethylidene)-5-hydroxypyrazine-2-carboxamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amiloride Tablets

General Notices

Action and use

Sodium channel blocker; potassium-sparing diuretic.

DEFINITION

Amiloride Tablets contain Amiloride Hydrochloride Dihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous amiloride hydrochloride, $C_6H_8ClN_7O,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing the equivalent of 0.5 mg of anhydrous amiloride hydrochloride with 100 mL of *0.1 M hydrochloric acid* and filter. The *light absorption* of the filtrate, Appendix II B, in the range 230 to 380 nm exhibits two maxima, at 285 nm and at 361 nm.

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (5).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *acetonitrile* and 3 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 17.5 mg of anhydrous amiloride hydrochloride with 10 mL of a mixture of 1 volume of *acetonitrile* and 3 volumes of *water*, disperse with the aid of ultrasound for 5 minutes and centrifuge.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.0010% w/v of *methyl 3,5-diamino-6-chloropyrazine-2-carboxylate BPCRS*.

(5) 0.175% w/v of *amiloride hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of the peak due to amiloride.

MOBILE PHASE

5 volumes of *tetramethylammonium hydroxide solution*, 250 volumes of *acetonitrile* and 745 volumes of *water*, the pH of the mixture being adjusted to 7.0 using a mixture of 1 volume of *orthophosphoric acid* and 9 volumes of *water*.

Adjust the concentration of *acetonitrile* so that, in the chromatogram obtained with solution (4), the retention time of methyl 3,5-diamino-6-chloropyrazine-2-carboxylate is 5 to 6 minutes (an increase in the concentration of *acetonitrile* reduces the retention time). Adjust the concentrations of tetramethylammonium hydroxide and orthophosphoric acid so that, in the chromatogram obtained with solution (2), the retention time of amiloride is 9 to 12 minutes keeping the pH at 7.0 (an increase in the concentrations reduces the retention time).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *signal-to-noise ratio* of the peak due to amiloride in the chromatogram obtained is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* is not greater than the area of the peak due to methyl 3,5-diamino-6-chloropyrazine-2-carboxylate in the chromatogram obtained with solution (4) (0.6%).

Disregard any peak with an area less than 0.1 times the area of the peak due to methyl 3,5-diamino-6-chloropyrazine-2-carboxylate in the chromatogram obtained with solution (4) (0.06%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing the equivalent of 10 mg of anhydrous amiloride hydrochloride add 10 mL of *methanol* and shake for 10 minutes. Add 60 mL of 0.1M *sodium hydroxide*, shake for 30 minutes and dilute to 100 mL with 0.1M *sodium hydroxide*. Immediately transfer 4 mL of the resulting solution to a stoppered centrifuge tube and add 10 mL of 0.1M *sodium hydroxide* and 20 mL of *tributyl orthophosphate* that has been washed with *water* before use. Shake vigorously for 2 minutes and centrifuge for 5 minutes. Remove the upper layer and repeat the extraction with a further 20 mL of the water-washed tributyl orthophosphate. To the combined extracts add 2 mL of *methanol* and sufficient of the water-washed tributyl orthophosphate to produce 50 mL and centrifuge to remove traces of water. Measure the *absorbance* of the resulting solution at the maximum at 363 nm, Appendix II B, using in the reference cell a mixture of 48 volumes of the water-washed tributyl orthophosphate and 2 volumes of *methanol*. Calculate the content of $C_6H_8ClN_7O$,HCl taking 692 as the value of A(1%, 1 cm) at the maximum at 363 nm.

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrousamiloride hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

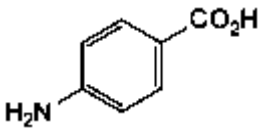
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aminobenzoic Acid

General Notices

(4-Aminobenzoic Acid, Ph. Eur. monograph 1687)



$C_7H_7NO_2$ 137.1 *150-13-0*

Action and use

Skin protective.

Ph Eur

DEFINITION

4-Aminobenzoic acid.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (*2.2.14*): 186 °C to 189 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *4-aminobenzoic acid CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *4-aminobenzoic acid CRS* in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *4-nitrobenzoic acid R* in 10 mL of reference solution (a).

Plate Suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm as the coating substance.

Mobile phase *glacial acetic acid R*, *hexane R*, *methylene chloride R* (5:20:75 *V/V/V*).

Application 1 µL.

Development Over a path of 10 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_5 (*2.2.2, Method II*).

Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution Dissolve 25.0 mg of *4-nitrobenzoic acid R* and 25.0 mg of *benzocaine R* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.12 m, Ø = 4.0 mm,

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 20 volumes of a mixture of 70 volumes of *acetonitrile R* and 80 volumes of *methanol R*, and 80 volumes of a solution containing 1.5 g/L of *potassium dihydrogen phosphate R* and 2.5 g/L of *sodium octanesulfonate R* adjusted to pH 2.2 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 20 µL.

Run time 11 times the retention time of 4-aminobenzoic acid.

Relative retention With reference to 4-aminobenzoic acid (retention time = about 3 min): impurity A = about 4; impurity B = about 9.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.2 per cent),

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.2 per cent),

— *any other impurity*: not more than 0.5 times the area of the peak due to impurity A in the chromatogram obtained with the reference solution (0.1 per cent),

— *total*: not more than 2.5 times the area of the peak due to impurity A in the chromatogram obtained with the reference solution (0.5 per cent),

— *disregard limit*: 0.1 times the area of the peak due to impurity A in the chromatogram obtained with the reference solution (0.02 per cent).

Impurity C and impurity D

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 20.0 mg of *lauric acid R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Test solution Dissolve 1.000 g of the substance to be examined in 10.0 mL of an 84 g/L solution of *sodium hydroxide R* and extract with 2 quantities, each of 10 mL, of *methylene chloride R*. Combine and wash with 5 mL of *water R*; filter through *anhydrous sodium sulfate R*. Wash the filter with *methylene chloride R*. Evaporate in a water-bath at 50-60 °C to obtain a volume of about 1-5 mL. Add 1.0 mL of the internal standard solution and dilute to 10.0 mL with *methylene chloride R*.

Reference solution (a) Dissolve 20.0 mg of *aniline R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 20.0 mg of *p-toluidine R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dilute 0.50 mL of reference solution (a), 0.50 mL of reference solution (b) and 10.0 mL of the internal standard solution to 100.0 mL with *methylene chloride R*.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *material*: fused silica,

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.0 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 4	130
	4 - 6.5	130 → 180
	6.5 - 11.5	180
Injection port		280
Detector		300

Detection Flame ionisation.

Injection 2 µL; inject the test solution and reference solution (c).

Retention time Internal standard = about 9.5 min.

Limits:

— *impurity C*: calculate the ratio (*R*) of the area of the peak due to impurity C to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (c); calculate the ratio of the area of the peak due to impurity C to the area of the peak due to the internal standard from the chromatogram obtained with the test solution: this ratio is not greater than *R* (10 ppm),

— *impurity D*: calculate the ratio (*R*) of the area of the peak due to impurity D to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (c); calculate the ratio of the area of the peak due to impurity D to the area of the peak due to the internal standard from the chromatogram obtained with the test solution: this ratio is not greater than *R* (10 ppm).

Iron (*2.4.9*)

Maximum 40 ppm.

Dissolve 0.250 g in 3 mL of *ethanol (96 per cent) R* and dilute to 10.0 mL with *water R*.

www.webofpharma.com

https://thuocngocanh.com/

Water (*2.5.12*)

Maximum 0.2 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

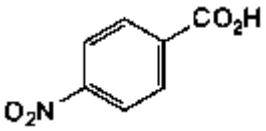
Dissolve 0.100 g with heating in 50 mL of *carbon dioxide-free water R*. Titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 13.71 mg of $C_7H_7NO_2$.

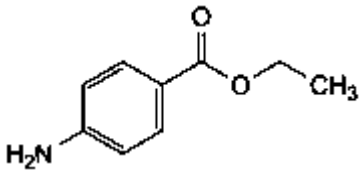
STORAGE

Protected from light.

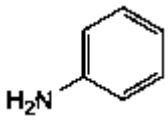
IMPURITIES



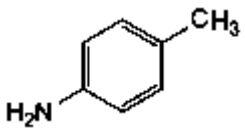
A. 4-nitrobenzoic acid,



B. ethyl 4-aminobenzoate (benzocaine),



C. aniline,



D. 4-methylaniline (*p*-toluidine).

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Aminocaproic Acid

General Notices

(Ph. Eur. monograph 0874)

$C_6H_{13}NO_2$ 131.2 *60-32-2*

Action and use

Antifibrinolytic.

Ph Eur

DEFINITION

Aminocaproic acid contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 6-aminohexanoic acid, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, freely soluble in water, slightly soluble in ethanol (96 per cent).

It melts at about 205 °C with decomposition.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *aminocaproic acid CRS*. Examine the substances prepared as discs.

B. Examine the chromatograms obtained in the test for ninhydrin-positive substances. The principal spot in the chromatogram obtained with the test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.5 g in 4 mL of a mixture of equal volumes of *dilute hydrochloric acid R* and *water R*. Evaporate to dryness by heating on a water-bath. Dry the residue in a desiccator. Dissolve the residue in about 2 mL of boiling *ethanol R*. Allow to cool and maintain at 4 °C to

www.webofpharma.com

https://thuocngocanh.com/

8 °C for 3 h. Filter under reduced pressure. The residue washed with about 10 mL of *acetone R* and dried at 60 °C for 30 min, melts (*2.2.14*) at 131 °C to 133 °C.

D. Dissolve about 5 mg in 0.5 mL of *distilled water R*. Add 3 mL of *dimethylformamide R* and 2 mL of *ascorbic acid solution R*. Heat on a water-bath. An orange colour develops.

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is colourless (*2.2.2, Method II*) and remains clear (*2.2.1*) on standing for 24 h.

pH (*2.2.3*)

The pH of solution S is 7.5 to 8.0.

Absorbance (*2.2.25*)

A. The absorbance of solution S at 287 nm is not more than 0.10 and at 450 nm is not more than 0.03.

B. Place 2.0 g in an even layer in a shallow dish 9 cm in diameter, cover and allow to stand at 98 °C to 102 °C for 72 h. Dissolve in *water R* and dilute to 10.0 mL with the same solvent. The absorbance of the solution at 287 nm is not more than 0.15 and at 450 nm is not more than 0.03.

Ninhydrin-positive substances

Examine by thin-layer chromatography (*2.2.27*), using a suitable silica gel as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 50 mL with *water R*.

Reference solution (a) Dissolve 10 mg of *aminocaproic acid CRS* in *water R* and dilute to 50 mL with the same solvent.

Reference solution (b) Dilute 5 mL of test solution (b) to 20 mL with *water R*.

Reference solution (c) Dissolve 10 mg of *aminocaproic acid CRS* and 10 mg of *leucine CRS* in *water R* and dilute to 25 mL with the same solvent.

Apply separately to the plate 5 µL of each solution. Allow the plate to dry in air. Develop over a path of 15 cm using a mixture of 20 volumes of *glacial acetic acid R*, 20 volumes of *water R* and 60 volumes of *butanol R*. Dry the plate in a current of warm air. Spray with *ninhydrin solution R* and heat at 100 °C to 105 °C for 15 min. Any spot in the chromatogram obtained with the test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated principal spots.

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 20 mL of *anhydrous acetic acid R*. Using 0.1 mL of *crystal violet solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from bluish-violet to bluish-green.

1 mL of *0.1 M perchloric acid* is equivalent to 13.12 mg of $C_6H_{13}NO_2$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

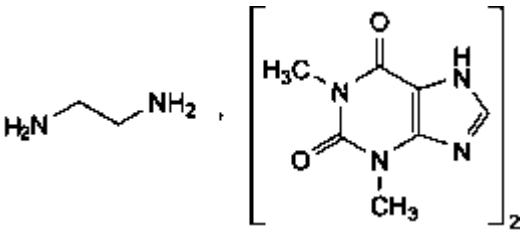
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Aminophylline

General Notices

(Theophylline-Ethylenediamine, Ph. Eur. monograph 0300)



$C_{16}H_{24}N_{10}O_4$ 420.4 *317-34-0*

Action and use

Non-selective phosphodiesterase inhibitor; treatment of reversible airways obstruction.

Preparations

Aminophylline Injection

Aminophylline Tablets

Aminophylline Prolonged-release Tablets

Ph Eur

DEFINITION

Content

— *theophylline* ($C_7H_8N_4O_2$; M_r 180.2): 84.0 per cent to 87.4 per cent (anhydrous substance);

— *ethylenediamine* ($C_2H_8N_2$; M_r 60.1): 13.5 per cent to 15.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellowish powder, sometimes granular, hygroscopic.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide), practically insoluble in anhydrous ethanol.

IDENTIFICATION

First identification: A, C, E.

Second identification: B, D, E.

Dissolve 1.0 g in 10 mL of *water R* and add 2 mL of *dilute hydrochloric acid R* dropwise with shaking. Filter. Use the precipitate for identification test A and the filtrate for identification test C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Precipitate, washed with *water R* and dried at 105 °C.

Comparison *theophylline CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.2 g of the substance to be examined in 2 mL of *water R* with heating and dilute to 10 mL with *methanol R*.

Reference solution Dissolve 0.2 g of *theophylline CRS* in 2 mL of *water R* with heating and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *acetone R*, *methylene chloride R*, *butanol R* (10:30:30:40 *V/V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To the filtrate add 0.2 mL of *benzoyl chloride R*, make alkaline with *dilute sodium hydroxide solution R* and shake vigorously. Filter the precipitate, wash with 10 mL of *water R*, dissolve in 5 mL of hot *ethanol (96 per cent) R* and add 5 mL of *water R*. A precipitate is formed, which, when washed and dried at 105 °C, melts (*2.2.14*) at 248 °C to 252 °C.

D. Dissolve 30 mg of the substance to be examined in 3 mL of *water R* and add 0.5 mL of a 10 g/L solution of *copper sulfate pentahydrate R*. A violet-purple colour is produced.

E. Water (see Tests).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, Method II).

Dissolve 0.5 g with gentle warming in 10 mL of carbon dioxide-free water R.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 47 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of theobromine R (impurity G) in the mobile phase, add 5 mL of the test solution and dilute to 100 mL with the mobile phase. Dilute 5 mL of this solution to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: irregular octadecylsilyl silica gel for chromatography R (7 µm).

Mobile phase Mix 7 volumes of acetonitrile R and 93 volumes of a 1.36 g/L solution of sodium acetate R containing 0.50 per cent *V/V* of glacial acetic acid R.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 µL.

Run time 3.5 times the retention time of theophylline.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to theophylline (retention time = about 6 min): impurity G = about 0.6.

System suitability Reference solution (b):

— resolution: minimum 2.0 between the peaks due to impurity G and theophylline.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 1.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Ethylenediamine

Dissolve 0.250 g in 30 mL of *water R*. Add 0.1 mL of *bromocresol green solution R*. Titrate with *0.1 M hydrochloric acid* until a green colour is obtained.

1 mL of *0.1 M hydrochloric acid* is equivalent to 3.005 mg of $C_2H_8N_2$.

Theophylline

Heat 0.200 g to constant mass in an oven at 135 °C. Dissolve the residue with heating in 100 mL of *water R*, allow to cool, add 20 mL of *0.1 M silver nitrate* and shake. Add 1 mL of *bromothymol blue solution R1*. Titrate with *0.1 M sodium hydroxide*.

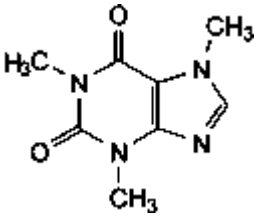
1 mL of *0.1 M sodium hydroxide* is equivalent to 18.02 mg of $C_7H_8N_4O_2$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

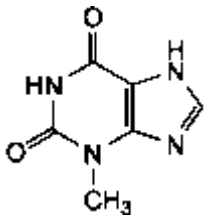
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G.*



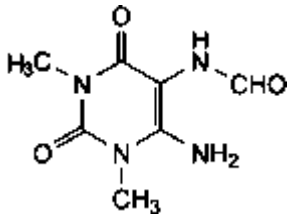
A. 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (caffeine),

www.webofpharma.com

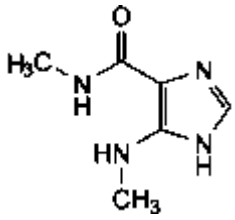
https://thuocngocanh.com/



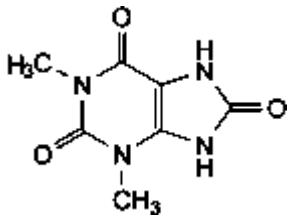
B. 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione,



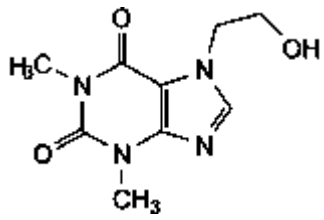
C. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



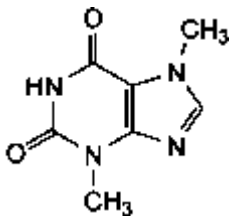
D. *N*-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide,



E. 1,3-dimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione,



F. 7-(2-hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (etofylline),



www.webofpharma.com

https://thuvienthuocngocanh.com/

G. 3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theobromine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

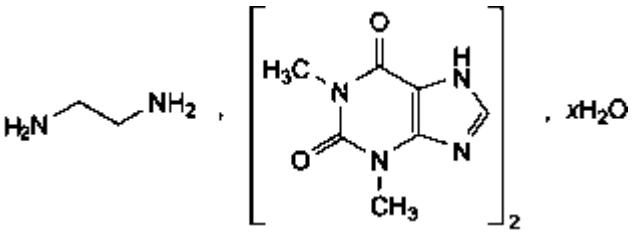
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Aminophylline Hydrate

General Notices

(Theophylline-Ethylenediamine Hydrate, Ph. Eur. monograph 0301)



$C_{16}H_{24}N_{10}O_4,xH_2O$ 420.4 (anhydrous substance) *72487-55-9*

Action and use

Non-selective phosphodiesterase inhibitor; treatment of reversible airways obstruction.

Preparations

Aminophylline Injection

Aminophylline Tablets

Aminophylline Prolonged-release Tablets

Ph Eur

DEFINITION

Content

— *theophylline* ($C_7H_8N_4O_2$; M_r 180.2): 84.0 per cent to 87.4 per cent (anhydrous substance);

— *ethylenediamine* ($C_2H_8N_2$; M_r 60.1): 13.5 per cent to 15.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or slightly yellowish powder, sometimes granular.

Solubility

Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide), practically insoluble in anhydrous ethanol.

IDENTIFICATION

First identification: A, C, E.

Second identification: B, D, E.

Dissolve 1.0 g in 10 mL of *water R* and add 2 mL of *dilute hydrochloric acid R* dropwise with shaking. Filter. Use the precipitate for identification test A and the filtrate for identification test C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Precipitate, washed with *water R* and dried at 105 °C.

Comparison *theophylline CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.2 g of the substance to be examined in 2 mL of *water R* with heating and dilute to 10 mL with *methanol R*.

Reference solution Dissolve 0.2 g of *theophylline CRS* in 2 mL of *water R* with heating and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *acetone R*, *methylene chloride R*, *butanol R* (10:30:30:40 *V/V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To the filtrate add 0.2 mL of *benzoyl chloride R*, make alkaline with *dilute sodium hydroxide solution R* and shake vigorously. Filter the precipitate, wash with 10 mL of *water R*, dissolve in 5 mL of hot *ethanol (96 per cent) R* and add 5 mL of *water R*. A precipitate is formed which, when washed and dried at 105 °C, melts (*2.2.14*) at 248 °C to 252 °C.

D. Dissolve 30 mg of the substance to be examined in 3 mL of *water R* and add 0.5 mL of a 10 g/L solution of *copper sulfate pentahydrate R*. A violet-purple colour is produced.

E. Water (see Tests).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, Method II).

Dissolve 0.5 g with gentle warming in 10 mL of *carbon dioxide-free water R*.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *theobromine R* (impurity G) in the mobile phase, add 5 mL of the test solution and dilute to 100 mL with the mobile phase. Dilute 5 mL of this solution to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: irregular *octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 7 volumes of *acetonitrile R* and 93 volumes of a 1.36 g/L solution of *sodium acetate R* containing 0.50 per cent *V/V* of *glacial acetic acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 µL.

Run time 3.5 times the retention time of theophylline.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to theophylline (retention time = about 6 min): impurity G = about 0.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity G and theophylline.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

3.0 per cent to 8.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Ethylenediamine

Dissolve 0.250 g in 30 mL of *water R*. Add 0.1 mL of *bromocresol green solution R*. Titrate with *0.1 M hydrochloric acid* until a green colour is obtained.

1 mL of *0.1 M hydrochloric acid* is equivalent to 3.005 mg of $C_2H_8N_2$.

Theophylline

Heat 0.200 g to constant mass in an oven at 135 °C. Dissolve the residue with heating in 100 mL of *water R*, allow to cool, add 20 mL of *0.1 M silver nitrate* and shake. Add 1 mL of *bromothymol blue solution R1*. Titrate with *0.1 M sodium hydroxide*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.02 mg of $C_7H_8N_4O_2$.

STORAGE

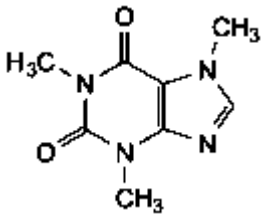
In a well-filled, airtight container, protected from light.

IMPURITIES

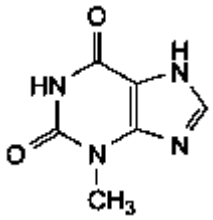
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G.*

www.webofpharma.com

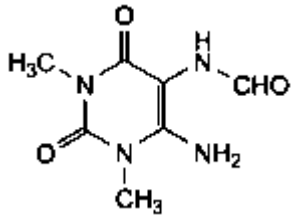
https://thuocngocanh.com/



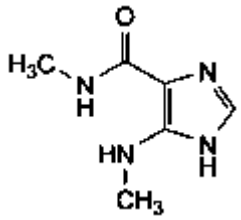
A. 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (caffeine),



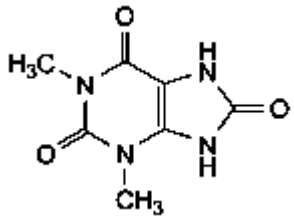
B. 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione,



C. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



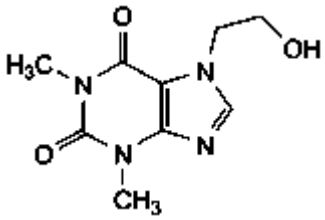
D. *N*-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide,



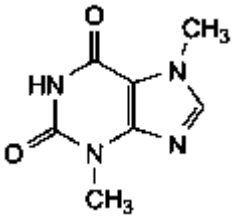
E. 1,3-dimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione,

www.webofpharma.com

https://thuocngocanh.com/



F. 7-(2-hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (etofylline),



G. 3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theobromine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aminophylline Injection

General Notices

Action and use

Non-selective phosphodiesterase inhibitor; treatment of reversible airways obstruction.

DEFINITION

Aminophylline Injection is a solution of Aminophylline or Aminophylline Hydrate in Water for Injections free from carbon dioxide.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of theophylline, $C_7H_8N_4O_2$

81.4 to 90.0% of the stated amount of aminophylline.

Content of ethylenediamine, $C_2H_8N_2$

Not more than 29.5% of the amount of anhydrous theophylline determined in the Assay for theophylline.

IDENTIFICATION

A. To a volume containing the equivalent of 0.1 g of aminophylline add 0.5 mL of 2M *hydrochloric acid* with constant stirring, allow to stand for a few minutes and filter. Wash the residue with small quantities of cold *water*, recrystallise from hot *water* and dry at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of theophylline *(RS 333)*.

B. To a volume containing the equivalent of 0.1 g of Aminophylline add 2 mL of a 1% w/v solution of *copper(II) sulfate* and shake. A purplish blue colour is produced.

C. Evaporate a volume containing the equivalent of 60 mg of aminophylline to dryness in a porcelain dish. To the residue add 1 mL of *hydrochloric acid* and 0.1 g of *potassium chlorate* and evaporate to dryness. A reddish residue is produced, which becomes purple on exposure to the vapour of 5M *ammonia*.

TESTS

Alkalinity

pH, 8.8 to 10.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (80%)*.

(1) Dilute the injection, if necessary, to produce a solution containing the equivalent of 0.01% w/v of aminophylline.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of solution (1) to 100 volumes. Further dilute 1 volume of this solution to 5 volumes.

(3) Dissolve 80 mg of *theobromine* (impurity G) in 5 mL of 0.2M *sodium hydroxide*, and dilute to 100 mL with *methanol (80%)*. Dilute 1 volume of the resulting solution and 1 volume of 0.08% w/v of *theophylline BPCRS* to 10 volumes, and further dilute 4 volumes to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 272 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of theophylline.

MOBILE PHASE

70 volumes of *acetonitrile* and 930 volumes of a 0.136% w/v solution of *sodium acetate* containing 0.50% v/v of *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to theophylline (retention time about 7 minutes) are: impurity C, about 0.2; impurity B, about 0.39; impurity D, about 0.45; impurity E, about 0.54; impurity G, about 0.6; impurity F, about 1.4; impurity A, about 2.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to theophylline and impurity G is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For theophylline

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (80%)*.

(1) Dilute the injection, if necessary, to produce a solution containing the equivalent of 0.01% w/v of aminophylline.

(2) 0.008% w/v of *theophylline BPCRS*.

(3) Dissolve 80 mg of *theobromine* (impurity G) in 5 mL of 0.2M *sodium hydroxide* and dilute to 100 mL with *methanol (80%)*. Dilute 1 volume of the resulting solution and 1 volume of 0.08% w/v of *theophylline BPCRS* to 10 volumes, and further dilute 4 volumes to 5 volumes.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_8N_4O_2$ in the injection using the declared content of $C_7H_8N_4O_2$ in *theophylline BPCRS*.

For ethylenediamine

To a volume containing the equivalent of 0.5 g of aminophylline add, if necessary, sufficient *water* to produce 20 mL and titrate with *0.05M sulfuric acid VS*, using *bromocresol green solution* as indicator, until the colour changes from blue to green. Each mL of *0.05M sulfuric acid VS* is equivalent to 3.005 mg of $C_2H_8N_2$. Calculate the weight of $C_2H_8N_2$ present for each g of $C_7H_8N_4O_2$ found.

LABELLING

When the injection is prepared from Aminophylline Hydrate, Theophylline or Theophylline Hydrate the strength is stated in terms of the equivalent amount of aminophylline in a suitable dose-volume.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aminophylline Hydrate.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aminophylline Prolonged-release Tablets

General Notices

Prolonged-release Aminophylline Tablets

Aminophylline Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Non-selective phosphodiesterase inhibitor; treatment of reversible airways obstruction.

DEFINITION

Aminophylline Prolonged-release Tablets contain Aminophylline or Aminophylline Hydrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Aminophylline. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of theophylline, $C_7H_8N_4O_2$

81.4 to 90.0% of the stated amount of aminophylline.

Content of ethylenediamine, $C_2H_8N_2$

13.5 to 15.0% of the stated amount of aminophylline.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 0.5 g of aminophylline with 20 mL of *water*, filter, add to the filtrate with constant stirring 1 mL of *2M hydrochloric acid*, allow to stand for a few minutes and again filter. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of theophylline *(RS 333)*.

B. Shake a quantity of the powdered tablets containing the equivalent of 0.25 g of aminophylline with 5 mL of *water* and filter. To 2 mL of the filtrate add 2 mL of a 1% w/v solution of *copper(II) sulfate* and shake. A purplish blue colour is produced.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.25 g of aminophylline with 50 mL of the mobile phase and add sufficient of the mobile phase to produce 100 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Further dilute 1 volume of this solution to 5 volumes with the mobile phase.

(3) Dissolve 10 mg of *theobromine* (impurity G) in the mobile phase, add 5 mL of solution (1) and dilute to 100 mL with the mobile phase. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (7 µm) (Lichrosorb RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 272 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3.5 times the retention time of theophylline.

MOBILE PHASE

7 volumes of *acetonitrile* and 93 volumes of a 0.136% w/v solution of *sodium acetate* containing 0.50% v/v of *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to theophylline (about 6 minutes) is: impurity G, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and theophylline is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than half times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For theophylline

Weigh and powder 20 tablets. Shake a quantity of the powder containing the equivalent of 80 mg of aminophylline with a mixture of 20 mL of 0.1M *sodium hydroxide* and 60 mL of *water* for 10 minutes, add sufficient *water* to produce 200 mL, mix and filter. Dilute 5 mL of the filtrate to 250 mL with 0.01M *sodium hydroxide* and measure the *absorbance* of the resulting solution at the maximum at 275 nm, Appendix II B. Calculate the content of $C_7H_8N_4O_2$ taking 650 as the value of A (1%, 1 cm) at the maximum at 275 nm.

www.webofpharma.com

https://thuocngocanh.com/

For ethylenediamine

Weigh and powder 20 tablets. Shake a quantity of the powder containing the equivalent of 0.3 g of aminophylline with 20 mL of *water*, heat to 50° for 30 minutes and titrate with *0.05M sulfuric acid VS*, using *bromocresol green solution* as indicator, until the colour changes from blue to green. Each mL of *0.05M sulfuric acid VS* is equivalent to 3.005 mg of $C_2H_8N_2$.

STORAGE

Aminophylline Prolonged-release Tablets should be kept in an airtight container and protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous aminophylline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aminophylline.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aminophylline Tablets

General Notices

Action and use

Non-selective phosphodiesterase inhibitor; treatment of reversible airways obstruction.

DEFINITION

Aminophylline Tablets contain Aminophylline or Aminophylline Hydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of theophylline, $C_7H_8N_4O_2$

81.4 to 90.0% of the stated amount of aminophylline.

Content of ethylenediamine, $C_2H_8N_2$

13.5 to 15.0% of the stated amount of aminophylline.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 0.5 g of aminophylline with 20 mL of *water*, filter, add to the filtrate with constant stirring 1 mL of *2M hydrochloric acid*, allow to stand for a few minutes and again filter. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of theophylline *(RS 333)*.

B. Shake a quantity of the powdered tablets containing the equivalent of 0.25 g of aminophylline with 5 mL of *water* and filter. To 2 mL of the filtrate add 2 mL of a 1% w/v solution of *copper(ii) sulfate* and shake. A purplish blue colour is produced.

TESTS

Dissolution of theophylline

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 7.0*, at a temperature of 37°, as the medium.

PROCEDURE

Withdraw a sample of 10 mL of the medium and filter. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Use the filtered dissolution medium, diluted with *phosphate buffer pH 7.0*, if necessary to produce a solution expected to contain 0.001% w/v of theophylline.

(2) 0.001% w/v solution of *theophylline BPCRS* in *phosphate buffer pH 7.0*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with particles of silica the surface of which has been modified with chemically-bonded phenyl groups (5 µm) (Apex Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 273 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of *methanol* and 55 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the total content of theophylline, $C_7H_8N_4O_2$, in the medium using the declared content of $C_7H_8N_4O_2$ in *theophylline BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.25 g of aminophylline with 50 mL of the mobile phase and add sufficient of the mobile phase to produce 100 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Further dilute 1 volume of this solution to 5 volumes with the mobile phase.

(3) Dissolve 10 mg of *theobromine* (impurity G) in the mobile phase, add 5 mL of solution (1) and dilute to 100 mL with the mobile phase. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (7 µm) (Lichrosorb RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 272 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3.5 times the retention time of theophylline.

MOBILE PHASE

7 volumes of *acetonitrile* and 93 volumes of a 0.136% w/v solution of *sodium acetate* containing 0.50% v/v of *glacial acetic acid*.

www.webofpharma.com

https://thuocngocanh.com/

When the chromatograms are recorded under the prescribed conditions the retention time relative to theophylline (about 6 minutes) is: impurity G, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity G and theophylline is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For theophylline

Weigh and powder 20 tablets. Shake a quantity of the powder containing the equivalent of 80 mg of aminophylline with a mixture of 20 mL of 0.1M *sodium hydroxide* and 60 mL of *water* for 10 minutes, add sufficient *water* to produce 200 mL, mix and filter. Dilute 5 mL of the filtrate to 250 mL with 0.01M *sodium hydroxide* and measure the *absorbance* of the resulting solution at the maximum at 275 nm, Appendix II B. Calculate the content of $C_7H_8N_4O_2$ taking 650 as the value of A (1%, 1 cm) at the maximum at 275 nm.

For ethylenediamine

Weigh and powder 20 tablets. Shake a quantity of the powder containing the equivalent of 0.3 g of aminophylline with 20 mL of *water*, heat to 50° for 30 minutes and titrate with *0.05M sulfuric acid VS*, using *bromocresol green solution* as indicator, until the colour changes from blue to green. Each mL of *0.05M sulfuric acid VS* is equivalent to 3.005 mg of $C_2H_8N_2$.

STORAGE

Aminophylline Tablets should be kept in an airtight container and protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous aminophylline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aminophylline.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

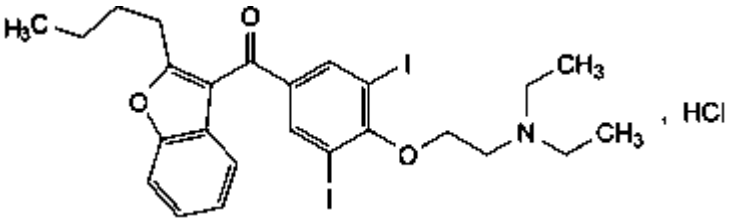
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amiodarone Hydrochloride

General Notices

(Ph. Eur. monograph 0803)



$C_{25}H_{30}ClI_2NO_3$ 682 *19774-82-4*

Action and use

Potassium channel blocker; class III antiarrhythmic.

Preparations

Amiodarone Infusion

Amiodarone Oral Suspension

Amiodarone Tablets

Ph Eur

DEFINITION

(2-Butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, fine, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *amiodarone hydrochloride CRS*.

B. It gives reaction (b) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution GY_5 or BY_5 (2.2.2, *Method II*).

Dissolve 1.0 g in *methanol R* and dilute to 20 mL with the same solvent.

pH (2.2.3)

3.2 to 3.8.

Dissolve 1.0 g in *carbon dioxide-free water R*, heating at 80 °C, cool and dilute to 20 mL with the same solvent.

Impurity H

Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use and keep protected from bright light.*

Test solution Dissolve 0.500 g of the substance to be examined in *methylene chloride R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *(2-chloroethyl)diethylamine hydrochloride R* (impurity H) in *methylene chloride R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with *methylene chloride R*.

Reference solution (b) Mix 2.0 mL of the test solution and 2.0 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *methanol R*, *methylene chloride R* (5:10:85 *V/V/V*).

Application 50 µL of the test solution and reference solution (a); 100 µL of reference solution (b).

Development Over 2/3 of the plate.

Drying In a current of cold air.

Detection Spray with *potassium iodobismuthate solution R1* and then with *dilute hydrogen peroxide solution R*; examine immediately in daylight.

System suitability Reference solution (b):

— the spot due to impurity H is clearly visible.

www.webofpharma.com

https://thuocngocanh.com/

Limit:

— *impurity H*: any spot due to impurity H is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.02 per cent).

Related substances

Liquid chromatography (2.2.29).

Buffer solution pH 4.9 To 800 mL of water R add 3.0 mL of glacial acetic acid R, adjust to pH 4.9 with dilute ammonia R1 and dilute to 1000 mL with water R.

Test solution Dissolve 0.125 g of the substance to be examined in a mixture of equal volumes of acetonitrile R and water R and dilute to 25.0 mL with the same mixture of solvents.

Reference solution Dissolve 5 mg of amiodarone impurity D CRS, 5 mg of amiodarone impurity E CRS and 5.0 mg of amiodarone hydrochloride CRS in methanol R and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with a mixture of equal volumes of acetonitrile R and water R.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase Buffer solution pH 4.9, methanol R, acetonitrile R (30:30:40 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time Twice the retention time of amiodarone.

Relative retention With reference to amiodarone (retention time = about 24 min): impurity A = about 0.26; impurity D = about 0.29; impurity E = about 0.37; impurity B = about 0.49; impurity C = about 0.55; impurity G = about 0.62; impurity F = about 0.69.

System suitability Reference solution:

— resolution: minimum 3.5 between the peaks due to impurities D and E.

Limits:

— *impurities A, B, C, D, E, F, G*: for each impurity, not more than the area of the peak due to amiodarone in the chromatogram obtained with the reference solution (0.2 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to amiodarone in the chromatogram obtained with the reference solution (0.10 per cent);

— *total*: not more than 2.5 times the area of the peak due to amiodarone in the chromatogram obtained with the reference solution (0.5 per cent);

— *disregard limit*: 0.25 times the area of the peak due to amiodarone in the chromatogram obtained with the reference solution (0.05 per cent).

Iodides

Maximum 150 ppm.

Prepare the test and reference solutions simultaneously.

Solution A Add 1.50 g of the substance to be examined to 40 mL of *water R* at 80 °C and shake until completely dissolved. Cool and dilute to 50.0 mL with *water R*.

Test solution To 15.0 mL of solution A add 1.0 mL of *0.1 M hydrochloric acid* and 1.0 mL of *0.05 M potassium iodate*. Dilute to 20.0 mL with *water R*. Allow to stand protected from light for 4 h.

Reference solution To 15.0 mL of solution A add 1.0 mL of *0.1 M hydrochloric acid*, 1.0 mL of an 88.2 mg/L solution of *potassium iodide R* and 1.0 mL of *0.05 M potassium iodate*. Dilute to 20.0 mL with *water R*. Allow to stand protected from light for 4 h.

Measure the absorbances (*2.2.25*) of the solutions at 420 nm, using a mixture of 15.0 mL of solution A and 1.0 mL of *0.1 M hydrochloric acid* diluted to 20.0 mL with *water R* as the compensation liquid. The absorbance of the test solution is not greater than half the absorbance of the reference solution.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying at 50 °C at a pressure not exceeding 0.3 kPa for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.600 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 75 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 68.18 mg of $C_{25}H_{30}ClI_2NO_3$.

STORAGE

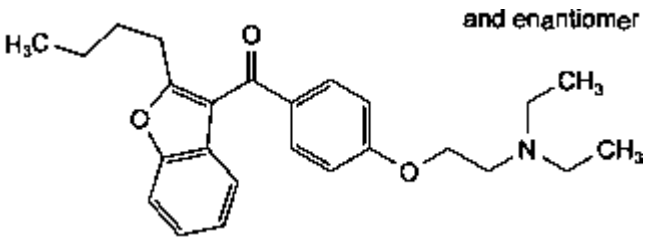
Protected from light, at a temperature not exceeding 30 °C.

www.webofpharma.com

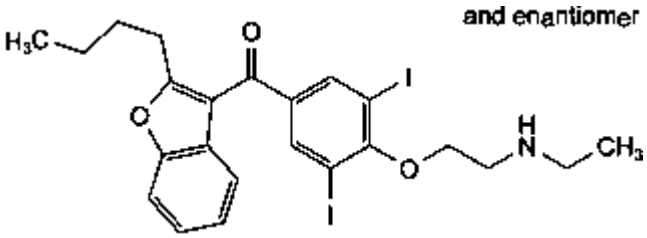
https://thuocngocanh.com/

IMPURITIES

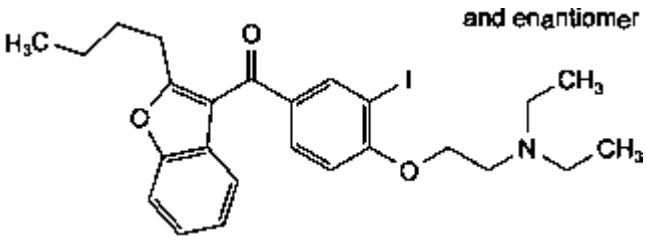
Specified impurities *A, B, C, D, E, F, G, H.*



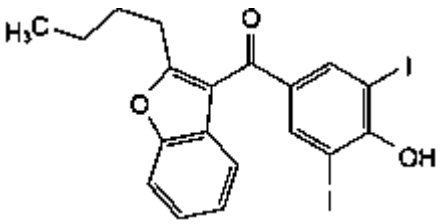
A. (2-butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]phenyl]methanone,



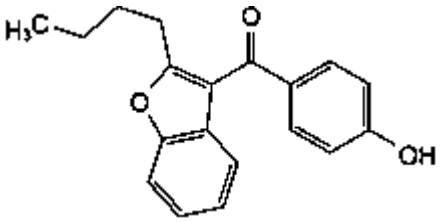
B. (2-butylbenzofuran-3-yl)[4-[2-(ethylamino)ethoxy]-3,5-diiodophenyl]methanone,



C. (2-butylbenzofuran-3-yl)[4-[2-(diethylamino)ethoxy]-3-iodophenyl]methanone,



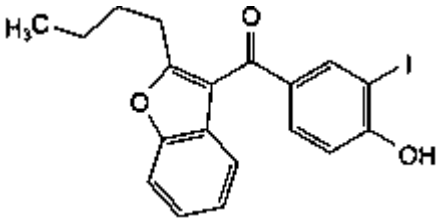
D. (2-butylbenzofuran-3-yl)(4-hydroxy-3,5-diiodophenyl)methanone,



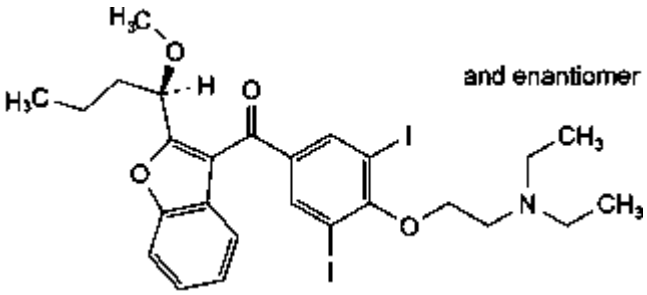
E. (2-butylbenzofuran-3-yl)(4-hydroxyphenyl)methanone,

www.webofpharma.com

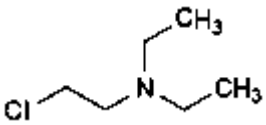
https://thuocngocanh.com/



F. (2-butylbenzofuran-3-yl)(4-hydroxy-3-iodophenyl)methanone,



G. [4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl][2-[(1*RS*)-1-methoxybutyl]benzofuran-3-yl]methanone,



H. 2-chloro-*N*,*N*-diethylethanamine (2-chlorotriethylamine, (2-chloroethyl)diethylamine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amiodarone Infusion

General Notices

Amiodarone Intravenous Infusion

Action and use

Potassium channel blocker; class III antiarrhythmic.

DEFINITION

Amiodarone Infusion is a sterile solution containing Amiodarone Hydrochloride. It is prepared by diluting Amiodarone Sterile Concentrate with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations.

AMIODARONE STERILE CONCENTRATE

DEFINITION

Amiodarone Sterile Concentrate is a sterile solution of Amiodarone Hydrochloride in a suitable diluent.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of amiodarone hydrochloride, $C_{25}H_{29}I_2NO_3,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a volume of the concentrate containing 0.3 g of Amiodarone Hydrochloride with three 25-mL quantities of *dichloromethane*. Dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate to dryness. To the residue add 2 mL of 1M *sodium hydroxide* and extract with 25 mL of *ether*. Dry the extract over *anhydrous sodium sulfate*, filter and evaporate to dryness. Dry the residue obtained under reduced pressure over *phosphorus pentoxide* and dissolve in 2.5 mL of *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of amiodarone *(RS 008)*.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak in the chromatogram obtained with solution (2).

TESTS

Colour of solution

www.webofpharma.com

https://thuocngocanh.com/

Not more intense than *reference solution* BY_4 or GY_4, Appendix IV B, Method II.

Iodides

Prepare a solution containing 1 volume *nitric acid*, 20 volumes of *water* and 80 volumes of *methanol* (solution A).

(1) Add 5.0 mL of a solution containing 0.0052% w/v of *potassium iodide* to a volume of the sterile concentrate containing 0.40 g of Amiodarone Hydrochloride and dilute to 50 mL with solution A.
(2) Dilute 10.0 mL of a solution containing 0.0052% w/v of *potassium iodide* to 50 mL with solution A.
Titrate solutions (1) and (2) with *0.001M silver nitrate VS* and determine the end point for each potentiometrically using a combined silver electrode. The volume used for the titration of solution (1) is not more than the volume required for the titration of solution (2) (500 ppm).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *acetonitrile (50%)*.

(1) Dilute a volume of the concentrate containing 50 mg of Amiodarone Hydrochloride to 20 mL.
(2) Dilute 1 volume of solution (1) to 500 volumes.
(3) 0.004% w/v of *amiodarone impurity D BPCRS*.
(4) 0.0005% w/v each of *amiodarone impurity D BPCRS* and *amiodarone impurity E EPCRS*.
(5) 0.1% w/v of *benzyl alcohol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 10 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 1.5 times the retention time of amiodarone.

MOBILE PHASE

Buffer solution pH 4.9. To 800 mL of *water*, add 3 mL of *glacial acetic acid*, adjust to pH 4.9 with *dilute ammonia R1* and dilute to 1000 mL with *water*.

30 volumes of *methanol*, 40 volumes of *acetonitrile* and 30 volumes of buffer solution pH 4.9.

When the chromatograms are recorded under the prescribed conditions the retention times relative to amiodarone (retention time about 24 minutes) are impurity D, about 0.3 and impurity E, about 0.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1.6%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak due to benzyl alcohol and any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *acetonitrile (50%)*.

(1) Dilute a volume of the concentrate containing 50 mg of Amiodarone Hydrochloride to 100 mL.
(2) 0.05% w/v of *amiodarone hydrochloride BPCRS*.
(3) 0.0005% w/v each of *amiodarone impurity D BPCRS* and *amiodarone impurity E EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{29}I_2NO_3$,HCl in the infusion using the declared content of $C_{25}H_{29}I_2NO_3$,HCl in *amiodarone hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those under Amiodarone Hydrochloride.

STORAGE

Amiodarone Sterile Concentrate should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amiodarone Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Potassium channel blocker; class III antiarrhythmic.

DEFINITION

Amiodarone Oral Suspension is a suspension of Amiodarone Hydrochloride in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of amiodarone hydrochloride, $C_{25}H_{29}I_2NO_3$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a volume of the oral suspension containing 0.3 g of Amiodarone Hydrochloride with three 25-mL quantities of *dichloromethane*. Dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate to dryness. To the residue add 2 mL of 1M *sodium hydroxide* and extract with 25 mL of *ether*. Dry the extract over *anhydrous sodium sulfate*, filter and evaporate to dryness. Dry the residue obtained under reduced pressure over *phosphorus pentoxide* for about 2 hours and dissolve in 2 mL of *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of amiodarone *(RS 008)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of *methanol* to a quantity of the oral suspension containing 50 mg of Amiodarone Hydrochloride; shake for 15 minutes, cool, add sufficient *methanol* to produce 50 mL, mix well and filter through a 0.45-µm nylon filter. Dilute 1 volume of the filtrate to 2 volumes

www.webofpharma.com

https://thuocngocanh.com/

with a mixture of equal volumes of *acetonitrile* and *water*.

(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume of the resulting solution to 10 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(3) Dilute 1 volume of solution (2) to 4 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(4) Dissolve 5 mg of *amiodarone impurity D BPCRS* and 5 mg of *amiodarone impurity E EPCRS* in *methanol* and dilute to 25 mL with the same solvent. Dilute 1 volume of the solution to 200 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice the retention time of the peak due to amiodarone.

MOBILE PHASE

30 volumes of *methanol*, 40 volumes of *acetonitrile* and 30 volumes of a mixture prepared in the following manner: to 800 mL of *water*, add 3 mL of *glacial acetic acid*, adjust to pH 4.9 with *dilute ammonia R1* and dilute to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time of amiodarone is about 24 minutes. The retention times relative to amiodarone are: impurity A, about 0.26; impurity D, about 0.29; impurity E, about 0.37; impurity B, about 0.49; impurity C, about 0.55; impurity G, about 0.62; impurity F, about 0.69.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 2.5 times the area of the peak due to impurity D in the chromatogram obtained with solution (4) (0.5%);

the area of any other *secondary peak* is not greater than the area of the peak due to amiodarone in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the peak due to amiodarone in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the peak due to amiodarone in the chromatogram obtained with solution (3) (0.05%).

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral suspension containing 10 mg of Amiodarone Hydrochloride with sufficient mobile phase to produce 50 mL. Dilute 1 volume of this solution to 2 volumes with the mobile phase.

(2) 0.01% w/v of *amiodarone hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 244 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of 0.01M *sodium perchlorate* and 55 volumes of *acetonitrile*, adjusted to pH 3.0 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{25}H_{29}I_2NO_3$,HCl, weight in volume, using the declared content of $C_{25}H_{29}I_2NO_3$,HCl in *amiodarone hydrochloride BPCRS*.

STORAGE

Amiodarone Oral Suspension should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A to G listed under Amiodarone Hydrochloride.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amiodarone Tablets

General Notices

Action and use

Potassium channel blocker; class III antiarrhythmic.

DEFINITION

Amiodarone Tablets contain Amiodarone Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of amiodarone hydrochloride, $C_{25}H_{29}I_2NO_3,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.3 g of Amiodarone Hydrochloride with 25 mL of *dichloromethane*, filter and evaporate the filtrate to dryness. To the residue add 2 mL of 1M *sodium hydroxide* and extract with 25 mL of *ether*. Dry the extract over *anhydrous sodium sulfate*, filter and evaporate to dryness. Dry the residue obtained under reduced pressure over *phosphorus pentoxide* and dissolve in 2.5 mL of *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of amiodarone *(RS 008)*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 50 mg of Amiodarone Hydrochloride with 50 mL of *methanol*, allow to cool and filter through a 0.45-µm PTFE filter. Dilute 1 volume of the solution to 2 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume of the resulting solution to 10 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(3) Dilute 1 volume of solution (2) to 4 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(4) Dissolve 10 mg each of *amiodarone impurity D BPCRS* and *amiodarone impurity E EPCRS* in *methanol* and dilute to 50 mL with the same solvent. Dilute 1 volume of the solution to 200 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS(2) is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature maintained at 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *methanol*, 40 volumes of *acetonitrile* and 30 volumes of a mixture prepared in the following manner: to 800 mL of *water*, add 3 mL of *glacial acetic acid*, adjust to pH 4.9 with *dilute ammonia R1* and dilute to 1000 mL with *water*.

SYSTEM SUITABILITY

The relative retention times with reference to amiodarone (retention time about 24 minutes) are: impurity A, about 0.26; impurity D, about 0.29; impurity E, about 0.37; impurity B, about 0.49; impurity C, about 0.55; impurity G, about 0.62; impurity F, about 0.69.

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 2.5 times the area of the peak due to impurity D in the chromatogram obtained with solution (4) (0.5%);

the area of any other *secondary peak* is not greater than the peak due to amiodarone in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the peak due to Amiodarone in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the peak due to amiodarone in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 50 mg of Amiodarone Hydrochloride with 100 mL of *methanol*, allow to cool and filter through a 0.45-µm PTFE filter. Dilute 1 volume of the solution to 5 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(2) Dilute 1 volume of a 0.05% w/v solution of *amiodarone hydrochloride BPCRS* in *methanol* to 5 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(3) Dissolve 10 mg each of *amiodarone impurity D BPCRS* and *amiodarone impurity E EPCRS* in *methanol* and dilute to 50 mL with the same solvent. Dilute 1 mL of the solution to 200 mL with a mixture of equal volumes of *acetonitrile* and *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{29}I_2NO_3$,HCl in the tablets using the declared content of $C_{25}H_{29}I_2NO_3$,HCl in *amiodarone hydrochloride BPCRS*.

STORAGE

Amiodarone Tablets should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

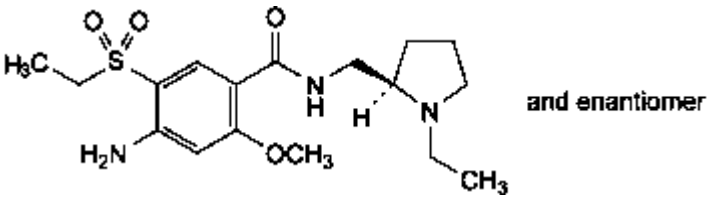
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amisulpride

General Notices

(Ph. Eur. monograph 1490)



and enantiomer

$C_{17}H_{27}N_3O_4S$ 369.5 *71675-85-9*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparations

Amisulpride Oral Solution

Amisulpride Tablets

Ph Eur

DEFINITION

4-Amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulfonyl)-2-methoxybenzamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol.

mp

www.webofpharma.com

https://thuocngocanh.com/

About 126 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison amisulpride CRS.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 1.0 g in 3 mL of a mixture of 1 volume of acetic acid R and 4 volumes of water R, and dilute to 20 mL with water R.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of sulpiride impurity A CRS (amisulpride impurity A) in methanol R and dilute to 25 mL with the same solvent. Dilute 2 mL of the solution to 20 mL with methanol R.

Reference solution (b) Dilute 1 mL of the test solution to 10 mL with reference solution (a).

Plate TLC silica gel G plate R.

Mobile phase 50 per cent *V/V* solution of concentrated ammonia R, anhydrous ethanol R, di-isopropyl ether R (10:25:65 *V/V/V*); use the upper layer obtained after shaking the mixture.

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with ninhydrin solution R and heat at 100-105 °C for 15 min.

Retardation factors Impurity A = about 0.2; amisulpride = about 0.5.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.1 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, methanol R, mobile phase A (12:16:72 *V/V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in 16 mL of methanol R, add 12 mL of acetonitrile R and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of amisulpride for system suitability CRS (containing impurity B) in 1 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.7 g of sodium octanesulfonate R in 930 mL of water for chromatography R and add 45.0 mL of a 5 per cent *V/V* solution of dilute sulfuric acid R; adjust to pH 2.3 with dilute sulfuric acid R and dilute to 1000 mL with water for chromatography R;

— *mobile phase B*: methanol R1 ;

— *mobile phase C*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 18	72	16	12
18 - 35	72 → 50	16 → 38	12

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to amisulpride (retention time = about 17 min): impurity B = about 1.1.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to amisulpride.

Calculation of percentage contents:

— for each impurity, use the concentration of amisulpride in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

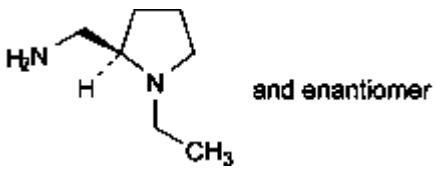
Dissolve 0.300 g with shaking in a mixture of 5 mL of *acetic anhydride R* and 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 36.95 mg of $C_{17}H_{27}N_3O_4S$.

IMPURITIES

Specified impurities *A*.

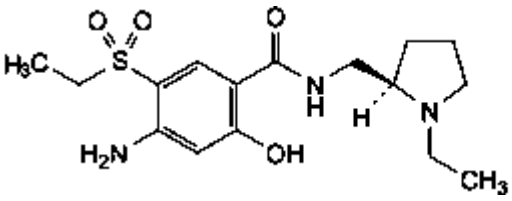
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F, G, H*.



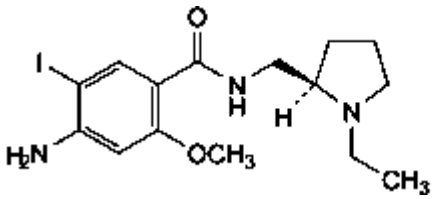
A. [(2*RS*)-1-ethylpyrrolidin-2-yl]methanamine,

www.webofpharma.com

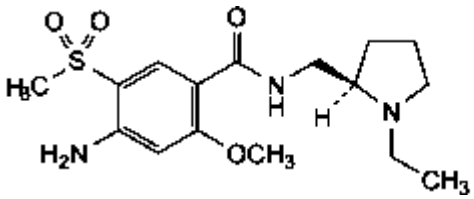
https://thuocngocanh.com/


and enantiomer

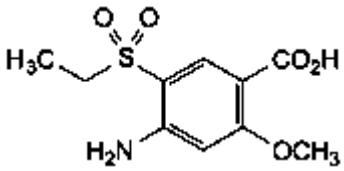
B. 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulfonyl)-2-hydroxybenzamide,


and enantiomer

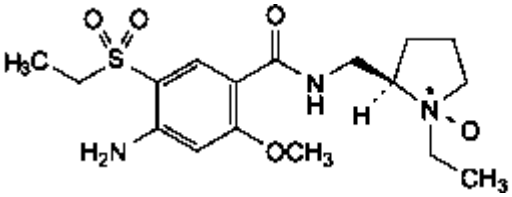
C. 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-iodo-2-methoxybenzamide,


and enantiomer

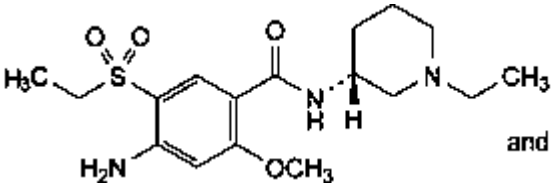
D. 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-5-(methylsulfonyl)benzamide,



E. 4-amino-5-(ethylsulfonyl)-2-methoxybenzoic acid,


and enantiomer

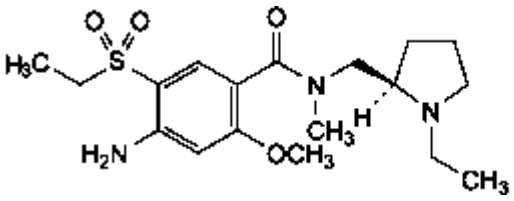
F. 4-amino-*N*-[[(2*RS*)-1-ethyl-1-oxidopyrrolidin-2-yl]methyl]-5-(ethylsulfonyl)-2-methoxybenzamide,


and enantiomer

G. 4-amino-*N*-[(3*RS*)-1-ethylpiperidin-3-yl]-5-(ethylsulfonyl)-2-methoxybenzamide,

www.webofpharma.com

https://thuocngocanh.com/



and enantiomer

H. 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulfonyl)-2-methoxy-*N*-methylbenzamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amisulpride Oral Solution

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Amisulpride Oral Solution contains Amisulpride.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of amisulpride, $C_{17}H_{27}N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the oral solution with sufficient *methanol* to produce a solution containing 0.5% w/v of Amisulpride.

(2) 0.5% w/v of *amisulpride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 4 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

Shake 10 volumes of 6M *ammonia*, 25 volumes of *ethanol* and 65 volumes of *di-isopropyl ether*, allow to separate and use the upper layer.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

www.webofpharma.com

https://thuocngocanh.com/

pH, 4.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the oral solution to produce a solution containing 0.1% w/v of Amisulpride.

(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of this solution to 5 volumes.

(3) 0.1% w/v of *amisulpride for system suitability BPCRS*.

(4) Dilute 1 volume of solution (2) to 4 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octylsilyl amorphous organosilica polymer* (5 µm) (Waters XTerra RP8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of amisulpride.

MOBILE PHASE

20 volumes of *methanol* and 80 volumes of a solution containing 0.68% w/v of *potassium dihydrogen phosphate* previously adjusted to pH 8.0 with 6M *ammonia*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to amisulpride (retention time about 10 minutes) are impurity E, about 0.2; impurity B, about 0.3; impurity F1, about 0.5 and impurity F2, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity E and impurity B is at least 2.0;

the *resolution* between the peaks due to impurity F1 and impurity F2 is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity B, impurity F1 and impurity F2 using the chromatogram obtained with solution (3) and the chromatogram supplied with *amisulpride for system suitability BPCRS*. Multiply the area of any peak corresponding to impurity B by a correction factor of 0.28. Combine the areas of the peaks corresponding to impurity F1 and impurity F2 (impurity F) and multiply by a correction factor of 1.45.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E, impurity B and impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the oral solution with sufficient mobile phase to produce a solution containing 0.01% w/v of Amisulpride.
(2) 0.01% w/v of *amisulpride BPCRS* in the mobile phase.
(3) 0.1% w/v of *amisulpride for system suitability BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity E and impurity B is at least 2.0;

the *resolution* between the peaks due to impurity F isomer 1 and impurity F isomer 2 is at least 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{17}H_{27}N_3O_4S$, weight in volume, using the declared content of amisulpride in *amisulpride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include:

B. 4-amino-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-5-(ethylsulfonyl)-2-hydroxybenzamide;
E. 4-amino-5-(ethylsulfonyl)-2-methoxybenzoic acid;
F. 4-amino-*N*-[[(2*RS*)-1-ethyl-1-oxidopyrrolidin-2-yl]methyl]-5-(ethylsulfonyl)-2-methoxybenzamide (observed as two peaks due to enantiomers F1 and F2).

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amisulpride Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Amisulpride Tablets contain Amisulpride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of amisulpride, $C_{17}H_{27}N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 100 mg of Amisulpride with 10 mL of *dichloromethane*, mix with the aid of ultrasound and filter. Evaporate the filtrate to dryness at a temperature not exceeding 30°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of amisulpride (*RS 462*).

TESTS

Dissolution

Complies with the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, diluted with the dissolution medium if necessary to produce a solution containing 0.0011% w/v of Amisulpride, at the maximum at about 280 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a 0.0011% w/v solution of *amisulpride BPCRS* in 0.1M *hydrochloric acid* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of amisulpride, $C_{17}H_{27}N_3O_4S$, in the medium from the absorbances obtained and using the declared content of $C_{17}H_{27}N_3O_4S$, in *amisulpride BPCRS*.

LIMITS

The amount of amisulpride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of powdered tablets containing 0.4 g of Amisulpride with 90 mL of the mobile phase, add sufficient mobile phase to produce 100 mL and filter (using an ash-free filter paper). Dilute 1 volume of the filtrate to 4 volumes.
(2) Dilute 1 volume of solution (1) to 100 volumes, and dilute 1 volume of this solution to 5 volumes.
(3) 0.1% w/v of *amisulpride for system suitability BPCRS*.
(4) Dilute 1 volume of solution (2) to 4 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octylsilyl amorphous organosilica polymer* (5 µm) (Waters XTerra RP8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 3 times the retention time of amisulpride.

MOBILE PHASE

20 volumes of *methanol* and 80 volumes of a solution containing 0.68% w/v of *potassium dihydrogen orthophosphate* previously adjusted to pH 8.0 with 6M *ammonia*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to amisulpride (retention time about 10 minutes) are impurity E, about 0.2; impurity B, about 0.3; impurity F1, about 0.5 and impurity F2, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity E and impurity B is at least 2.0;

the *resolution* between the peaks due to impurity F isomer 1 and impurity F isomer 2 is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity B, impurity F1 and impurity F2 using the chromatogram obtained with solution (3) and the chromatogram supplied with *amisulpride for system suitability BPCRS*. Multiply the area of

www.webofpharma.com

https://thuocngocanh.com/

any peak corresponding to impurity B by a correction factor of 0.28. Combine the areas of the 2 isomer peaks corresponding to impurity F1 and impurity F2 (impurity F) and multiply by a correction factor of 1.45.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E, impurity B and impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) Shake a quantity of powdered tablets containing 0.4 g of Amisulpride with 90 mL of the mobile phase, add sufficient mobile phase to produce 100 mL and filter (using an ash-free filter paper). Dilute 1 volume of filtrate to 40 volumes.
(2) 0.01% w/v of *amisulpride BPCRS*.
(3) 0.1% w/v of *amisulpride for system suitability BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity E and impurity B is at least 2.0;

the *resolution* between the peaks due to impurity F isomer 1 and impurity F isomer 2 is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{27}N_3O_4S$ in the tablets using the declared content of amisulpride in *amisulpride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include:

B. 4-amino-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-5-(ethylsulfonyl)-2-hydroxybenzamide;
E. 4-amino-5-(ethylsulfonyl)-2-methoxybenzoic acid;

www.webofpharma.com

https://thuocngocanh.com/

F. 4-amino-*N*-[[(2*RS*)-1-ethyl-1-oxidopyrrolidin-2-yl]methyl]-5-(ethylsulfonyl)-2-methoxybenzamide (observed as two peaks due to enantiomers F1 and F2).

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

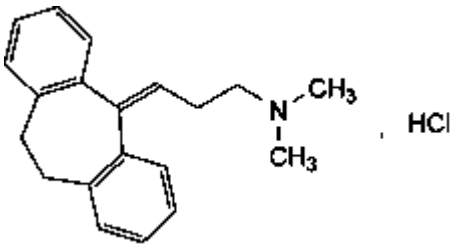
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amitriptyline Hydrochloride

General Notices

(Ph. Eur. monograph 0464)



$C_{20}H_{24}ClN$ 313.9 *549-18-8*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparations

Amitriptyline Tablets

Amitriptyline Oral Solution

Ph Eur

DEFINITION

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or colourless crystals.

Solubility

Freely soluble in water, in ethanol (96 per cent) and in methylene chloride.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *amitriptyline hydrochloride CRS*.

B. 20 mg gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, *Method II*).

Dissolve 1.25 g in *water R* and dilute to 25 mL with the same solvent.

Acidity or alkalinity

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *dibenzosuberone CRS* (impurity A) and 5.0 mg of *cyclobenzaprine hydrochloride CRS* (impurity B) in 5.0 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of a 5.23 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 7.0 with *phosphoric acid R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time 3 times the retention time of amitriptyline.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to amitriptyline (retention time = about 14 min): impurity B = about 0.9; impurity A = about 2.2.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity B and amitriptyline.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *impurity A*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to amitriptyline in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the peak due to amitriptyline in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the peak due to amitriptyline in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 30 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.39 mg of $C_{20}H_{24}ClN$.

STORAGE

Protected from light.

IMPURITIES

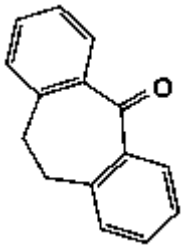
Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

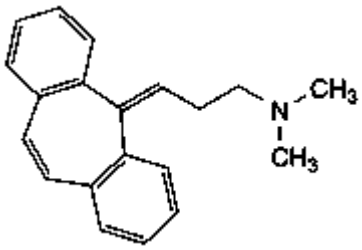
www.webofpharma.com

https://thuocngocanh.com/

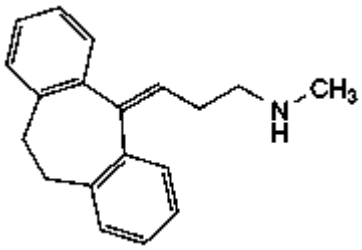
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E, F, G.



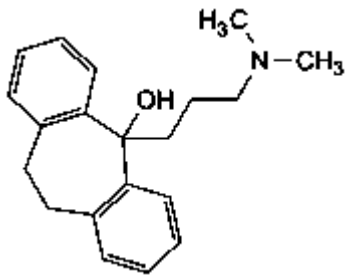
A. 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-one (dibenzosuberone),



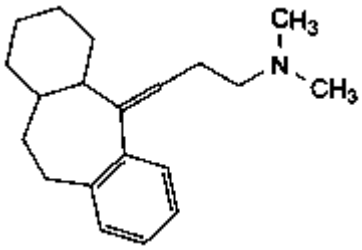
B. 3-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-amine (cyclobenzaprine),



C. 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (nortriptyline),



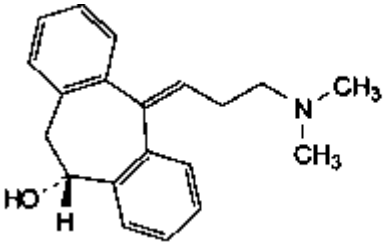
D. 5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol,



www.webofpharma.com

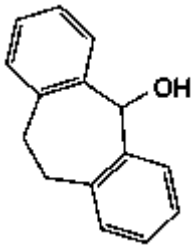
https://thuocngocanh.com/

E. *N*,*N*-dimethyl-3-(1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propan-1-amine,



its (*E*)-isomer and their enantiomers

F. (5*EZ*,10*RS*)-5-[3-(dimethylamino)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-10-ol,



G. 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol (dibenzosuberol).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amitriptyline Oral Solution

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Amitriptyline Oral Solution is a solution of Amitriptyline Hydrochloride in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of amitriptyline hydrochloride, $C_{20}H_{23}N,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in 1 volume of 2M *hydrochloric acid* and 9 volumes of *ethanol(96%)*.

(1) Dilute a quantity of the oral solution containing 50 mg of Amitriptyline Hydrochloride to 25 mL.

(2) 0.2% w/v of *amitriptyline hydrochloride BPCRS*.

(3) 0.4% w/v each of *amitriptyline hydrochloride BPCRS* and *nortriptyline hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *diethylamine*, 15 volumes of *ethyl acetate* and 85 volumes of *cyclohexane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and colour to that of the principal spot in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

ACIDITY

pH, 2.5 to 3.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the oral solution containing 50 mg of Amitriptyline Hydrochloride to 50 mL.
(2) Dilute 1 volume of solution (1) to 100 volumes, further dilut1 2 volume of this solution to 5 volumes.
(3) 0.001% w/v of *amitriptyline hydrochloride BPCRS*, 0.001% w/v of *cyclobenzaprine hydrochloride BPCRS* (impurity B) and 0.0002% w/v of *dibenzosuberone BPCRS* (impurity A).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar embedded octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (Waters X-Terra RP 18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 10 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for 3.5 times the retention time of amitriptyline.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of a 0.523% w/v solution of *dipotassium hydrogen orthophosphate*, previously adjusted to pH 7.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to amitriptyline (retention time about 12 minutes) are: impurity B, about 0.9 and impurity A, about 2.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between cyclobenzaprine and amitriptyline is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to dibenzosuberone is not greater than the area of the peak due to dibenzosuberone in the chromatogram obtained with solution (3) (0.2%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to cyclobenzaprine is not greater than 0.2 times the area of the peak due cyclobenzaprine in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of impurities is not greater than 0.50%;

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the oral solution containing 10 mg of Amitriptyline Hydrochloride to 100 mL.

(2) 0.01% w/v of *amitriptyline hydrochloride BPCRS*.

(3) 0.001% w/v of *amitriptyline hydrochloride BPCRS*, 0.001% w/v of *cyclobenzaprine hydrochloride BPCRS* and 0.0002% w/v of *dibenzosuberone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between cyclobenzaprine and amitriptyline is at least 2.0.

DETERMINATION OF CONTENT

Determine the weight per mL of the Oral Solution, Appendix V G, and calculate the content of $C_{20}H_{23}N$,HCl, weight in volume, using the declared content of $C_{20}H_{23}N$,HCl in *amitriptyline hydrochloride BPCRS*.

STORAGE

Amitriptyline Oral Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Amitriptyline Hydrochloride*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amitriptyline Tablets

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Amitriptyline Tablets contain Amitriptyline Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of amitriptyline hydrochloride, $C_{20}H_{23}N,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 20 mg of Amitriptyline Hydrochloride with 10 mL of *acetone*, filter and evaporate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of amitriptyline hydrochloride *(RS 501)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, *Appendix XII B1*.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, *Appendix III D*, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium if necessary, to produce a solution expected to contain 0.0011% w/v of Amitriptyline Hydrochloride.

(2) 0.0011% w/v of *amitriptyline hydrochloride BPCRS* in the dissolution medium.

(3) 0.001% w/v each of *amitriptyline hydrochloride BPCRS* and *cyclobenzaprine hydrochloride BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer for chromatography* (5µm) (Waters X-Terra RP 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of a 0.523% w/v solution of *dipotassium hydrogen orthophosphate*, previously adjusted to pH 7.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cyclobenzaprine hydrochloride and amitriptyline hydrochloride is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{20}H_{23}N$,HCl in the medium using the declared content of $C_{20}H_{23}N$,HCl in *amitriptyline hydrochloride BPCRS*.

LIMITS

The amount of $C_{20}H_{23}N$,HCl released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the powdered tablets containing 50 mg of Amitriptyline Hydrochloride with 25 mL of the mobile phase, dilute to 50 mL with the same solvent and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes, further dilute 1 volume of this solution to 5 volumes.

(3) 0.001% w/v of *amitriptyline hydrochloride BPCRS*, 0.001% w/v of *cyclobenzaprine hydrochloride BPCRS* (impurity B) and 0.00025% w/v of *dibenzosuberone BPCRS* (impurity A).

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used with an injection volume of 10 µL and, for solution (1), a run time of 3 times the retention time of the peak due to amitriptyline.

When the chromatograms are recorded under the prescribed conditions the retention times relative to amitriptyline (retention time about 12 minutes) are; impurity B, about 0.9 and impurity A, about 2.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and amitriptyline is at least 2.0.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak corresponding to dibenzosuberone is not greater than the area of the peak due to dibenzosuberone in the chromatogram obtained with solution (3) (0.25%);

the area of any peak corresponding to cyclobenzaprine hydrochloride is not greater than 0.2 times the area of the peak due to cyclobenzaprine hydrochloride in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not more than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of impurities is not greater than 0.50%;

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) *For film-coated tablets* Add 50 mL of 0.1M *hydrochloric acid* to 10 tablets, shake vigorously until the tablets are completely disintegrated, add 100 mL of *methanol* and shake for 30 minutes. Dilute the suspension to 200 mL with *methanol*, centrifuge and dilute a volume of the supernatant liquid containing 25 mg of Amitriptyline Hydrochloride to 100 mL with *methanol (50%)*.
For sugar-coated tablets Weigh and powder 20 tablets. Shake a quantity of the powder containing 50 mg of Amitriptyline Hydrochloride with 50 mL of 0.1M *hydrochloric acid* for 30 minutes, add 100 mL of *methanol* and shake for 30 minutes. Dilute the suspension to 200 mL with *water*, centrifuge and use the supernatant liquid.
(2) Dissolve 50 mg of *amitriptyline hydrochloride BPCRS* in 10 mL of *methanol* and dilute to 200 mL with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 239 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.03M *sodium hexanesulfonate* in a mixture of equal volumes of *water* and *acetonitrile*, adjusted to pH 4.5 by the addition of *glacial acetic acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{23}N$,HCl in the tablets using the declared content of $C_{20}H_{23}N$,HCl in *amitriptyline hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Amitriptyline Hydrochloride.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

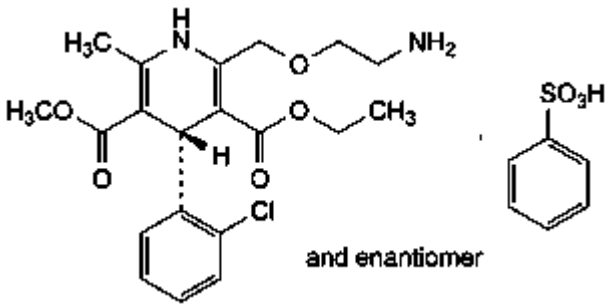
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amlodipine Besilate

General Notices

(Ph. Eur. monograph 1491)



$C_{26}H_{31}ClN_2O_8S$ 567.1 *111470-99-6*

Action and use

Calcium channel blocker.

Preparations

Amlodipine Besilate Tablets

Amlodipine Oral Solution

Ph Eur

DEFINITION

3-Ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl benzenesulfonate esters are genotoxic and are potential impurities in amlodipine besilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general method 2.5.41. *Methyl, ethyl and isopropyl benzenesulfonate in active substances* is available to assist manufacturers.

CHARACTERS

https://thuocngocanh.com/

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in 2-propanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *amlodipine besilate CRS*.

TESTS

Optical rotation (*2.2.7*)

-0.10° to + 0.10°.

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.5 mg of *amlodipine impurity B CRS* and 2.5 mg of *amlodipine impurity G CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 2.5 mg of *amlodipine for peak identification CRS* (containing impurities D, E and F) in 5 mL of the mobile phase.

Reference solution (d) Dissolve 5.0 mg of *amlodipine impurity A CRS* in *acetonitrile R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (e) Dissolve 50.0 mg of *amlodipine besilate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase 2.3 g/L solution of *ammonium acetate R*, *methanol R* (30:70 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 237 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b), (c) and (d).

Run time Twice the retention time of amlodipine.

Identification of impurities Use the chromatogram supplied with *amlodipine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D, E and F; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A.

Relative retention With reference to amlodipine (retention time = about 20 min): impurity G = about 0.21; impurity B = about 0.25; impurity D = about 0.5; impurity F = about 0.8; impurity E = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities G and B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity F = 0.7;

— *impurity D*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.15 per cent);

— *impurities E, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: maximum 0.8 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to benzene sulfonate (relative retention = about 0.14).

Water (*2.5.12*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (e).

Calculate the percentage content of $C_{26}H_{31}ClN_2O_8S$ taking into account the assigned content of *amlodipine besilate CRS*.

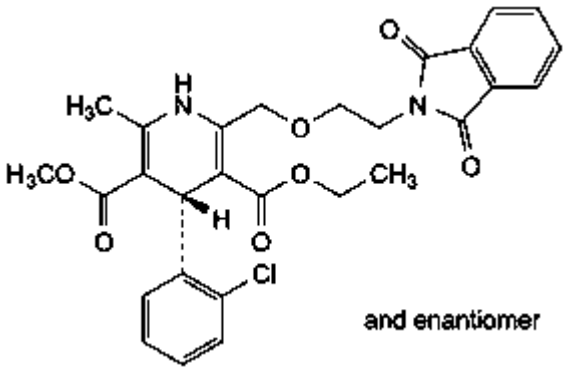
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, D, E, F.*

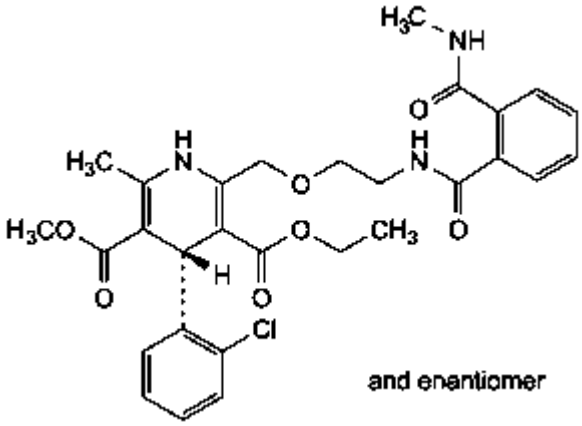
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, G, H.*



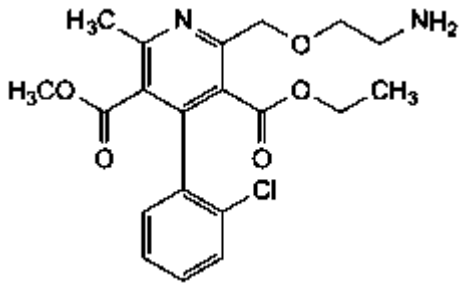
A. 3-ethyl 5-methyl (4*RS*)-4-(2-chlorophenyl)-2-[[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethoxy]methyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate,

www.webofpharma.com

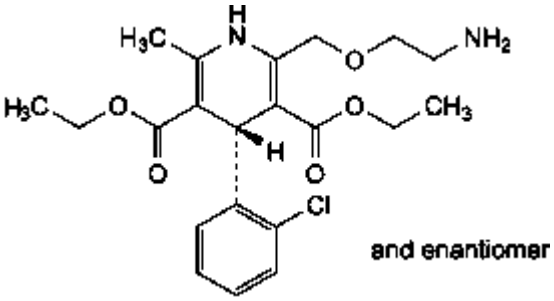
https://thuocngocanh.com/



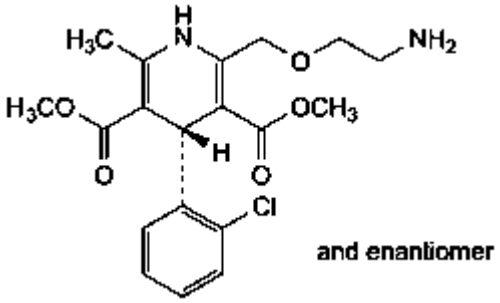
B. 3-ethyl 5-methyl (4*RS*)-4-(2-chlorophenyl)-6-methyl-2-[[2-[[2-(methylcarbamoyl)benzoyl]amino]ethoxy]methyl]-1,4-dihydropyridine-3,5-dicarboxylate,



D. 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methylpyridine-3,5-dicarboxylate,



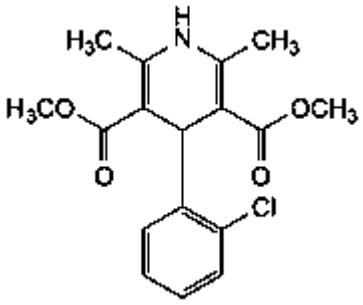
E. diethyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate,



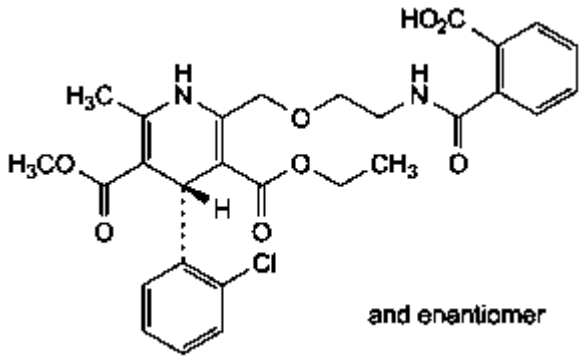
F. dimethyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate,

www.webofpharma.com

https://thuocngocanh.com/



G. dimethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,



H. 2-[[2-[[(4*RS*)-4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl]methoxy]ethyl]carbamoyl]benzoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amlodipine Besilate Tablets

General Notices

Action and use

Calcium channel blocker.

DEFINITION

Amlodipine Besilate Tablets contain Amlodipine Besilate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of amlodipine, $C_{20}H_{25}ClN_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 50 mg of amlodipine with 10 mL of *methanol*, filter and evaporate to dryness. Dry the residue at 40° to 60°. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the *reference spectrum* of amlodipine besilate *(RS 489)*. The absence of peaks at about 1570 cm^{-1}, 1345 cm^{-1} and 875 cm^{-1} distinguishes between amlodipine maleate *(RS 491)*. The presence of peaks at about 995 cm^{-1}, and 730 cm^{-1}, and the absence of a peak at about 780 cm^{-1}, distinguishes between amlodipine mesilate *(RS 490)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 with a PTFE-coated or non-metallic paddle, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.01M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 20 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, diluted with the dissolution medium if necessary, to produce a solution expected to contain the equivalent of 0.00056% w/v of amlodipine, at 238 nm, Appendix II B using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.00078% w/v solution of *amlodipine besilate BPCRS* in dissolution medium using dissolution medium in the reference cell.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of amlodipine, $C_{20}H_{25}ClN_2O_5$, in the medium from the absorbances obtained and using the declared content of $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$ in *amlodipine besilate BPCRS*.

Each mg of $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$ is equivalent to 0.7211 mg of $C_{20}H_{25}ClN_2O_5$.

LIMITS

The amount of amlodipine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 45 volumes of 0.03M *potassium dihydrogen orthophosphate* and 55 volumes of *methanol*.

(1) Disperse a quantity of the powdered tablets containing the equivalent of 25 mg of amlodipine in 10 mL of *water*. Add 50 mL of solution A and mix with the aid of ultrasound for at least 20 minutes. Allow to cool, and dilute to 100 mL with solution A. Centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume to 5 volumes.

(3) 0.025% w/v of *amlodipine for peak identification EPCRS*.

(4) 0.00025% w/v of *amlodipine impurity 1 BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (2.6 µm) (Kinetex C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 10 µL of each solution.

Mobile phase A 45 volumes of 0.03M *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*, and 55 volumes of *methanol*.

Mobile phase B 30 volumes of 0.03M *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*, and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to amlodipine (retention time about 8 minutes) are: impurity D, about 0.5; impurity F, about 0.7; impurity E, about 1.5; impurity G, about 1.7; impurity B, about 2.0; impurity 1, about 2.1 and impurity A, about 3.5.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-8	100	0	isocratic

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
8-13	100→0	0→100	linear gradient
13-34	0	100	isocratic
34-35	0→100	100→0	linear gradient
35-45	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity F and amlodipine is at least 5.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) due to impurities D and E using the chromatogram obtained with solution (3) and identify any peak due to impurity 1 using the chromatogram obtained with solution (4). Multiply the area of any peaks corresponding to impurity D and impurity 1 by a correction factor of 2.9 and any peak corresponding to impurity E by a correction factor of 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D or impurity 1 is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B 15 volumes of *acetonitrile*, 35 volumes of *methanol* and 50 volumes of 0.7% v/v of *triethylamine* in *water*, adjusted to pH 3.0 with *orthophosphoric acid*.

(1) Disperse with the aid of ultrasound 10 whole tablets in 150 mL of solution B and dilute to produce 500 mL with the same solution. Filter through a 0.45-µm nylon filter and dilute the filtrate with sufficient solution B to produce a solution containing 0.0012% w/v of amlodipine.
(2) 0.0017% w/v of *amlodipine besilate BPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of 0.7% v/v of *triethylamine* in *water*, adjusted to pH 3.0 with *orthophosphoric acid*, 35 volumes of *acetonitrile* and 35 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to amlodipine is less than 2.5.

DETERMINATION OF CONTENT

Calculate the content of amlodipine, $C_{20}H_{25}ClN_2O_5$, in the tablets using the declared content of $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$ in *amlodipine besilate BPCRS*.

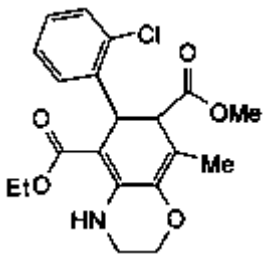
Each mg of $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$ is equivalent to 0.7211 mg of $C_{20}H_{25}ClN_2O_5$.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of amlodipine.

IMPURITIES

The impurities limited by the requirements of this monograph include A, B, D, E, F and G listed under Amlodipine Besilate and:



1. 5-ethyl 7-methyl 6-(2-chlorophenyl)-8-methyl-3,4,6,7-tetrahydro-2*H*-1,4-benzoxazine-5,7-dicarboxylate

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amlodipine Oral Solution

General Notices

Action and use

Calcium channel blocker.

DEFINITION

Amlodipine Oral Solution contains Amlodipine Besilate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of amlodipine, $C_{20}H_{25}ClN_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the oral solution containing the equivalent of 5 mg of amlodipine with 20 mL of *dichloromethane* for 30 minutes. Centrifuge, allow to separate and use the lower layer.

(2) 0.035% w/v of *amlodipine besilate BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *octadecylsilyl silica gel* (Macherey Nagel RP-18 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (366 nm)*.

MOBILE PHASE

2 volumes of a 10% w/v solution of *ammonia*, 4 volumes of *methanol* and 17 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to the principal spot in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in a mixture of 45 volumes of 0.03M *potassium dihydrogen orthophosphate* and 55 volumes of *methanol*.

(1) Dilute a quantity of the oral solution to produce a solution containing the equivalent of 0.025% w/v of amlodipine.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.025% w/v of *amlodipine for peak identification EPCRS*.

(4) 0.00025% w/v of *amlodipine impurity 1 BPCRS*

(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (2.6 µm) (Kinetex C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 10 µL of each solution.

Mobile phase A 45 volumes of 0.03M *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*, and 55 volumes of *methanol*.

Mobile phase B 30 volumes of 0.03M *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*, and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to amlodipine (retention time about 8 minutes) are: impurity D, about 0.5; impurity F, about 0.7; impurity E, about 1.5; impurity G, about 1.7; impurity B, about 2.0; impurity 1, about 2.1; and impurity A, about 3.5.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-8	100	0	isocratic
8-13	100→0	0→100	linear gradient
13-34	0	100	isocratic
34-35	0→100	100→0	linear gradient
35-45	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity F and amlodipine is at least 5.5;

www.webofpharma.com

https://thuocngocanh.com/

in the chromatogram obtained with solution (5), the *signal-to-noise ratio* of the peak due to impurity 1 is at least 60.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) due to impurities D, E and F using the chromatogram obtained with solution (3) and identify any peak due to impurity 1 using the chromatogram obtained with solution (4). Multiply the area of any peaks corresponding to impurity D and impurity 1 by a correction factor of 2.9 and any peak corresponding to impurity E by a correction factor of 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

the area of any peak corresponding to impurity E or F is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in a mixture of 45 volumes of 0.03M *potassium dihydrogen orthophosphate* and 55 volumes of *methanol*.

(1) Dilute a weighed quantity of the oral solution to produce a solution containing the equivalent of 0.005% w/v of amlodipine.
(2) 0.0069% w/v of *amlodipine besilate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (2.6 µm) (Kinetex C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 238 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

45 volumes of 0.03M *potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*, and 55 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention time of amlodipine besilate is about 8 minutes.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to amlodipine is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of amlodipine, $C_{20}H_{25}ClN_2O_5$, weight in volume using the declared content of $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$ in *amlodipine besilate BPCRS*.

Each mg of $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$ is equivalent to 0.7211 mg of $C_{20}H_{25}ClN_2O_5$.

STORAGE

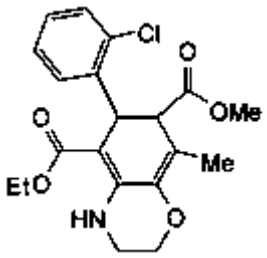
Amlodipine Oral Solution should be stored at a temperature of 2° to 8°.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of amlodipine.

IMPURITIES

The impurities limited by the requirements of this monograph include A, B, D, E, F and G listed under Amlodipine Besilate and:



1. 5-ethyl 7-methyl 6-(2-chlorophenyl)-8-methyl-3,4,6,7-tetrahydro-2*H*-1,4-benzoxazine-5,7-dicarboxylate

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

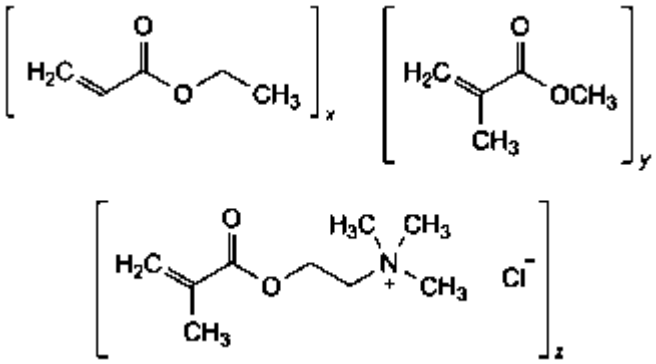
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Ammonio Methacrylate Copolymer (Type A)

General Notices

(Ph. Eur. monograph 2081)



Action and use

Excipient.

Ph Eur

DEFINITION

Poly[ethyl propenoate-*co*-methyl 2-methylprop-2-enoate-*co*-*N*,*N*,*N*-trimethyl-2-[(2-methylprop-2-enoyl)oxy]ethan-1-aminium chloride] having a mean relative molecular mass of about 150 000.

The ratio of ethyl acrylate (ethyl propenoate) groups to methyl methacrylate (methyl 2-methylprop-2-enoate) groups to ammonio methacrylate (*N*,*N*,*N*-trimethyl-2-[(2-methylprop-2-enoyl)oxy]ethan-1-aminium chloride) groups is about 1:2:0.2.

Content of ammonio methacrylate groups 8.9 per cent to 12.3 per cent (dried substance).

CHARACTERS

Appearance

Colourless to white or almost white granules or powder.

Solubility

www.webofpharma.com

https://nhathuocngocanh.com/

Practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride giving clear to cloudy solutions. Due to the polymeric nature of the substance, a stirring time of up to 5 h may be necessary.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ammonio methacrylate copolymer CRS*.

B. Viscosity (see Tests).

C. It complies with the limits of the assay.

TESTS

Solution S

Dissolve a quantity of the substance to be examined corresponding to 12.5 g of the dried substance in a mixture of 35.0 g of *acetone R* and 52.5 g of *2-propanol R*.

Viscosity (2.2.10)

Maximum 15 mPa·s, determined on solution S.

Apparatus Rotating viscometer.

Dimensions:

— *spindle*: diameter = 25.15 mm; height = 90.74 mm; shaft diameter = 4.0 mm;

— *cylinder*: diameter = 27.62 mm; height = 0.135 m.

Stirring speed 30 r/min.

Volume of solution 16 mL of solution S.

Temperature 20 °C.

Appearance of a film

Spread 2 mL of solution S evenly on a glass plate. Upon drying a clear film is formed.

Monomers

Liquid chromatography (2.2.29).

Solution A Dissolve 3.5 g of *sodium perchlorate R* in *water R* and dilute to 100 mL with the same solvent.

Test solution Dissolve 5.00 g of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent. To 10.0 mL of this solution add 5.0 mL of solution A, dropwise, while continuously stirring. Remove the precipitated polymer by centrifugation. Use the

www.webofpharma.com

https://thuocngocanh.com/

clear supernatant .

Reference solution Dissolve 50.0 mg of *ethyl acrylate R* and 10.0 mg of *methyl methacrylate R* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*. Add 10 mL of this solution to 5 mL of solution A.

Column:

— *size*: *l* = 0.12 m, Ø = 4.6 mm;

— *stationary phase*: irregular *end-capped octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 20 volumes of *methanol R2* and 80 volumes of *water for chromatography R* previously ajusted to pH 2.0 with *phosphoric acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 202 nm.

Injection 50 µL.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to impurity A and impurity B.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (100 ppm);

— *impurity B*: not more than 2.5 times the area of the corresponding peak in the chromatogram obtained with the reference solution (50 ppm).

Methanol (*2.4.24, System A*)

Maximum 1.5 per cent.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 5 h.

ASSAY

Dissolve 1.000 g in 75 mL of *glacial acetic acid R* at about 50 °C within about 30 min. Allow to cool to room temperature and add 25 mL of a 6 g/L solution of *copper acetate R* in *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

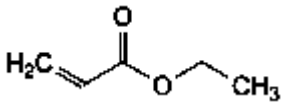
1 mL of *0.1 M perchloric acid* is equivalent to 20.77 mg of $C_9H_{18}O_2NCl$ (ammonio methacrylate groups).

IMPURITIES

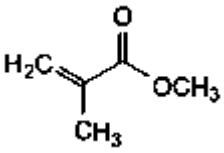
www.webofpharma.com

https://thuocngocanh.com/

Specified impurities *A, B.*



A. ethyl propenoate (ethyl acrylate),



B. methyl 2-methylprop-2-enoate (methyl methacrylate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuvienthuocngocanh.com/

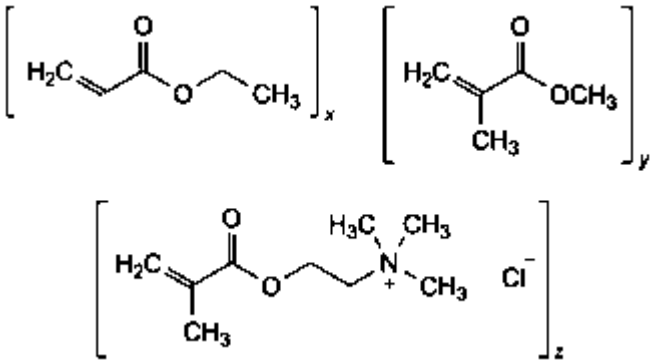
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Ammonio Methacrylate Copolymer (Type B)

General Notices

(Ph. Eur. monograph 2082)



Action and use

Excipient.

Ph Eur

DEFINITION

Poly[ethyl propenoate-*co*-methyl 2-methylprop-2-enoate-*co*-*N*,*N*,*N*-trimethyl-2-[(2-methylprop-2-enoyl)oxy]ethan-1-aminium chloride] having a mean relative molecular mass of about 150 000.

The ratio of ethyl acrylate (ethyl propenoate) groups to methyl methacrylate (methyl 2-methylprop-2-enoate) groups to ammonio methacrylate (*N*,*N*,*N*-trimethyl-2-[(2-methylprop-2-enoyl)oxy]ethan-1-aminium chloride) groups is about 1:2:0.1.

Content of ammonio methacrylate groups 4.5 per cent to 7.0 per cent (dried substance).

CHARACTERS

Appearance

Colourless to white or almost white granules or powder.

Solubility

www.webofpharma.com

https://thuvienthuocngocanh.com/

Practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride giving clear to cloudy solutions. Due to the polymeric nature of the substance, a stirring time of up to 5 h may be necessary.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ammonio methacrylate copolymer CRS*.

B. Viscosity (see Tests).

C. It complies with the limits of the assay.

TESTS

Solution S

Dissolve a quantity of the substance to be examined corresponding to 12.5 g of the dried substance in a mixture of 35.0 g of *acetone R* and 52.5 g of *2-propanol R*.

Viscosity (2.2.10)

Maximum 15 mPa·s, determined on solution S.

Apparatus Rotating viscometer.

Dimensions:

— *spindle*: diameter = 25.15 mm; height = 90.74 mm; shaft diameter = 4.0 mm;

— *cylinder*: diameter = 27.62 mm; height = 0.135 m.

Stirring speed 30 r/min.

Volume of solution 16 mL of solution S.

Temperature 20 °C.

Appearance of a film

Spread 2 mL of solution S evenly on a glass plate. Upon drying a clear film is formed.

Monomers

Liquid chromatography (2.2.29).

Solution A Dissolve 3.5 g of *sodium perchlorate R* in *water R* and dilute to 100 mL with the same solvent.

Test solution Dissolve 5.00 g of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent. To 10.0 mL of this solution add 5.0 mL of solution A, dropwise, while continuously stirring. Remove the precipitated polymer by centrifugation. Use the

www.webofpharma.com

https://thuocngocanh.com/

clear supernatant .

Reference solution Dissolve 50.0 mg of *ethyl acrylate R* and 10.0 mg of *methyl methacrylate R* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*. Add 10 mL of this solution to 5 mL of solution A.

Column:

— *size*: *l* = 0.12 m, Ø = 4.6 mm;

— *stationary phase*: irregular *end-capped octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 20 volumes of *methanol R2* and 80 volumes of *water for chromatography R* previously ajusted to pH 2.0 with *phosphoric acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 202 nm.

Injection 50 µL.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to impurity A and impurity B.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (100 ppm);

— *impurity B*: not more than 2.5 times the area of the corresponding peak in the chromatogram obtained with the reference solution (50 ppm).

Methanol (*2.4.24, System A*)

Maximum 1.5 per cent.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 5 h.

ASSAY

Dissolve 2.000 g in 75 mL of *glacial acetic acid R* at about 50 °C within about 30 min. Allow to cool to room temperature and add 25 mL of a 6 g/L solution of *copper acetate R* in *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

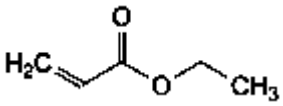
1 mL of *0.1 M perchloric acid* is equivalent to 20.77 mg of $C_9H_{18}O_2NCl$ (ammonio methacrylate groups).

IMPURITIES

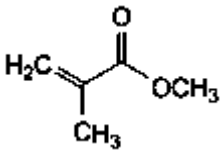
www.webofpharma.com

https://thuvienthuocngocanh.com/

Specified impurities *A, B.*



A. ethyl propenoate (ethyl acrylate),



B. methyl 2-methylprop-2-enoate (methyl methacrylate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ammonium Bicarbonate

General Notices

(Ammonium Hydrogen Carbonate, Ph. Eur. monograph 1390)

NH_4HCO_3 79.1 *1066-33-7*

Action and use

Expectorant.

Preparations

Aromatic Ammonia Solution

Strong Ammonium Acetate Solution

Aromatic Ammonia Spirit

Ph Eur

DEFINITION

Content

98.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

Fine, white or almost white, crystalline powder or white or almost white crystals, slightly hygroscopic.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

It volatilises rapidly at 60 °C. The volatilisation takes place slowly at ambient temperatures if the substance is slightly moist. It is in a state of equilibrium with ammonium carbamate.

IDENTIFICATION

A. It gives the reaction of carbonates and bicarbonates (*2.3.1*).

B. Dissolve 50 mg in 2 mL of *water R*. The solution gives the reaction of ammonium salts (*2.3.1*).

www.webofpharma.com

https://thietbiuocngocanh.com/

TESTS

Solution S

Dissolve 14.0 g in 100 mL of *distilled water R*. Boil to remove the ammonia, allow to cool and dilute to 100.0 mL with *distilled water R*.

Chlorides (2.4.4)

Maximum 70 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 70 ppm, determined on solution S.

Iron (2.4.9)

Maximum 40 ppm.

Dilute 1.8 mL of solution S to 10 mL with *water R*.

ASSAY

Dissolve cautiously 0.500 g in 50 mL of *carbon dioxide-free water R*. Titrate with *1 M hydrochloric acid*, determining the end-point potentiometrically (2.2.20). Read the volume added at the 2nd point of inflection, or at the point of inflection if only 1 point is detected.

1 mL of *1 M hydrochloric acid* is equivalent to 79.1 mg of NH_4HCO_3.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ammonium Bromide

General Notices

(Ph. Eur. monograph 1389)

NH_4Br 97.9 *12124-97-9*

Ph Eur

DEFINITION

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent).

It becomes yellow when exposed to light or air.

IDENTIFICATION

A. It gives reaction (a) of bromides (*2.3.1*).

B. 10 mL of solution S (see Tests) gives the reaction of ammonium salts (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

www.webofpharma.com

https://thuocngocanh.com/

To 10 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Bromates

To 10 mL of solution S add 1 mL of *starch solution R*, 0.1 mL of a 100 g/L solution of *potassium iodide R* and 0.25 mL of *0.5 M sulfuric acid* and allow to stand protected from light for 5 min. No blue or violet colour develops.

Chlorides and sulfates

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 0.400 g of the substance to be examined in 50 mL of *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 25.0 mL of test solution (a) to 50.0 mL with *water for chromatography R*.

Reference solution (a) To 25.0 mL of test solution (a) add 1.0 mL of *sulfate standard solution (10 ppm SO_4) R* and 12.0 mL of *chloride standard solution (50 ppm Cl) R* and dilute to 50.0 mL with *water for chromatography R*.

Reference solution (b) Dilute 10 mL of test solution (a) to 100 mL with *water for chromatography R*. To 2 mL of this solution add 8 mL of *chloride standard solution (50 ppm Cl) R* and dilute to 20 mL with *water for chromatography R*.

Blank solution *water for chromatography R*.

Column:

— *size*: *l* = 0.25 m, Ø = 2 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R2* (13 µm).

Mobile phase Dissolve 0.600 g of *potassium hydroxide R* in *water for chromatography R* and dilute to 1000 mL with the same solvent.

Flow rate 0.4 mL/min.

Detection Conductivity detector equipped with a suitable ion suppressor.

Injection 50 µL of test solution (b), reference solutions (a) and (b) and the blank solution.

Run time 2.5 times the retention time of bromide.

Retention time Chloride = about 5 min; bromide = about 8 min; sulfate = about 16 min.

System suitability Reference solution (b):

— *resolution*: minimum 8.0 between the peaks due to chloride and bromide.

Calculation of percentage contents:

www.webofpharma.com

https://thuocngocanh.com/

— for chlorides, use the concentration of chloride in reference solution (a); correct the area of the peak due to chloride in the chromatogram obtained with reference solution (a) by subtracting the area of the peak due to chloride in the chromatogram obtained with test solution (b);

— for sulfates, use the concentration of sulfate in reference solution (a); correct the area of the peak due to sulfate in the chromatogram obtained with reference solution (a) by subtracting the area of the peak due to sulfate in the chromatogram obtained with test solution (b).

Limits:

— *chlorides*: maximum 0.6 per cent;

— *sulfates*: maximum 0.01 per cent.

Iodides

To 5 mL of solution S add 0.15 mL of *ferric chloride solution R1* and 2 mL of *methylene chloride R*. Shake and allow to separate. The lower layer is colourless (*2.2.2, Method I*).

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Magnesium and alkaline-earth metals (*2.4.7*)

Maximum 200 ppm, calculated as Ca.

10.0 g complies with the test for magnesium and alkaline-earth metals. The volume of *0.01 M sodium edetate* used does not exceed 5.0 mL.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 80.0 mg in *water R*, add 5 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 9.794 mg of NH_4Br.

Calculate the percentage content of NH_4Br using the following expression:

www.webofpharma.com

https://thuvienthuocngocanh.com/

$a - 2.763\ b$

a	=	percentage content of NH_4Br and NH_4Cl obtained in the assay and calculated as NH_4Br;
b	=	percentage content of Cl obtained in the test for chlorides.

STORAGE

In an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ammonium Chloride

General Notices

(Ph. Eur. monograph 0007)

NH_4Cl 53.49 *12125-02-9*

Action and use

Used for the acidification of urine and to correct metabolic alkalosis.

Preparation

Ammonium Chloride Mixture

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water.

IDENTIFICATION

A. It gives reaction (a) of chlorides (*2.3.1*).

B. 10 mL of solution S (see Tests) gives the reaction of ammonium salts (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

https://thuocngocanh.com/

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of *methyl red solution R*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Bromides and iodides

To 10 mL of solution S add 0.1 mL of *dilute hydrochloric acid R* and 0.05 mL of *chloramine solution R*. After 1 min, add 2 mL of *chloroform R* and shake vigorously. The chloroform layer remains colourless (*2.2.2, Method I*).

Sulfates (*2.4.13*)

Maximum 150 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Calcium (*2.4.3*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.00 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Dissolve 1.000 g in 20 mL of *water R* and add a mixture of 5 mL of *formaldehyde solution R*, previously neutralised to *phenolphthalein solution R*, and 20 mL of *water R*. After 1-2 min, titrate slowly with *1 M sodium hydroxide*, using a further 0.2 mL of the same indicator.

1 mL of *1 M sodium hydroxide* is equivalent to 53.49 mg of NH_4Cl.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ammonium Chloride Mixture

General Notices

Ammonium Chloride Oral Solution

DEFINITION

Ammonium Chloride Mixture is an *oral solution* containing 10% w/v of Ammonium Chloride in a suitable vehicle containing Aromatic Ammonia Solution and Liquorice Liquid Extract.

Extemporaneous preparation

It is recently prepared according to the following formula.

Ammonium Chloride	100 g
Aromatic Ammonia Solution	50 mL
Liquorice Liquid Extract	100 mL
Water	Sufficient to produce 1000 mL

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ammonium chloride, NH_4Cl

9.50 to 10.66% w/v.

ASSAY

To 1 mL add 20 mL of *water* and titrate with *0.1M silver nitrate VS* determining the end point potentiometrically. Each mL of *0.1M silver nitrate VS* is equivalent to 5.349 mg of NH_4Cl.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

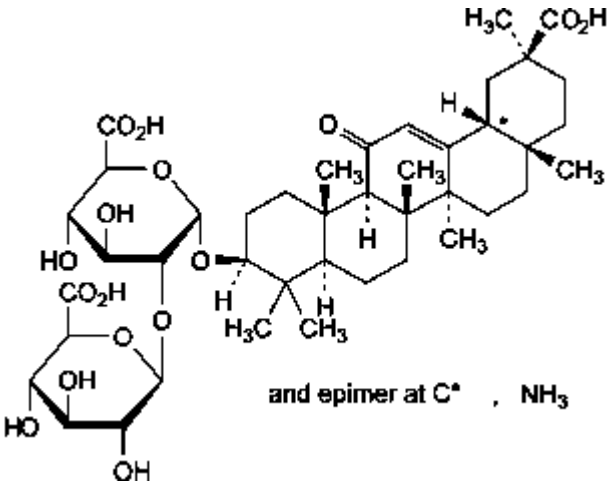
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ammonium Glycyrrhizinate

General Notices

(Ammonium Glycyrrhizate, Ph. Eur. monograph 1772)



$C_{42}H_{65}NO_{16}$ 840 *53956-04-0*

Ph Eur

DEFINITION

Mixture of ammonium 18α- and 18β-glycyrrhizate (ammonium salt of (20β)-3β-[[2-*O*-(β-D-glucopyranosyluronic acid)-α-D-glucopyranosyluronic acid]oxy]-11-oxoolean-12-en-29-oic acid), the 18β-isomer being the main component.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white, hygroscopic powder.

Solubility

Slightly soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ammonium glycyrrhizate CRS*.

B. Dissolve 0.1 g in 20 mL of *water R*, add 2 mL of *dilute sodium hydroxide solution R* and heat cautiously. On heating, the solution gives off vapours that may be identified by the alkaline reaction of wet litmus paper (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method I*).

Dissolve 1.0 g in *ethanol (20 per cent V/V) R* and dilute to 100.0 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 49.0 to + 54.0 (anhydrous substance).

Dissolve 0.5 g in *ethanol (50 per cent V/V) R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 50 mg of *ammonium glycyrrhizate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase *glacial acetic acid R*, *acetonitrile R*, *water R* (6:380:614 *V/V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 3 times the retention time of 18β-glycyrrhizic acid.

www.webofpharma.com

https://nhathuocngocanh.com/

Relative retention With reference to 18β-glycyrrhizic acid (retention time = about 8 min): impurity A = about 0.8; 18α-glycyrrhizic acid = about 1.2.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to 18β-glycyrrhizic acid and 18α-glycyrrhizic acid.

Limits:

— *18α-glycyrrhizic acid*: not more than twice the sum of the areas of the peaks in the chromatogram obtained with reference solution (a) (10.0 per cent),

— *impurity A*: not more than the sum of the areas of the peaks in the chromatogram obtained with reference solution (a) (5.0 per cent),

— *any other impurity*: for each impurity, not more than 0.4 times the sum of the areas of the peaks in the chromatogram obtained with reference solution (a) (2.0 per cent),

— *sum of other impurities*: not more than 1.4 times the sum of the areas of the peaks in the chromatogram obtained with reference solution (a) (7.0 per cent),

— *disregard limit*: 0.04 times the sum of the areas of the peaks in the chromatogram obtained with reference solution (a) (0.2 per cent).

Water (*2.5.12*)

Maximum 6.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.600 g in 60 mL of *anhydrous acetic acid R* heating at 80 °C if necessary. Cool. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 84.0 mg of $C_{42}H_{65}NO_{16}$.

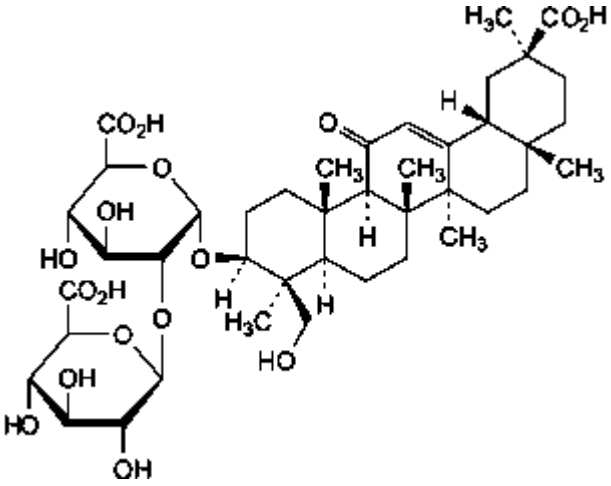
STORAGE

In an airtight container.

IMPURITIES

www.webofpharma.com

https://thuocngocanh.com/



A. (4β,20β)-3β-[[2-*O*-(β-D-glucopyranosyluronic acid)-α-D-glucopyranosyluronic acid]oxy]-23-hydroxy-11-oxoolean-12-en-29-oic acid (24-hydroxyglycyrrhizinic acid).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

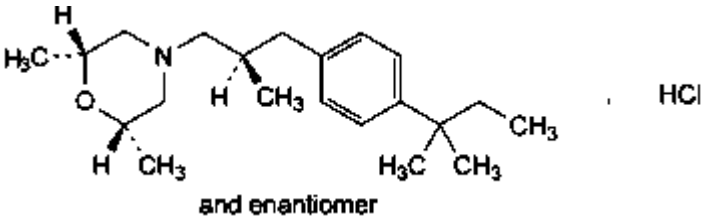
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amorolfine Hydrochloride

General Notices

(Ph. Eur. monograph 2756)



$C_{21}H_{36}ClNO$ 354.0 *78613-38-4*

Action and use

Antifungal.

Ph Eur

DEFINITION

(2*RS*,6*SR*)-2,6-Dimethyl-4-[(2*RS*)-2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]propyl]morpholine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, soluble in methanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *amorolfine hydrochloride CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. To 20 mg add 4.0 mL of *water R*, and acidify with *dilute nitric acid R*. A precipitate is formed. Centrifuge, and to 2 mL of the supernatant add 0.4 mL of *silver nitrate solution R1*. A curdled, white precipitate is formed. Centrifuge and wash the precipitate with 3 quantities, each of 1 mL, of *water R*. Suspend the precipitate in 2 mL of *water R* and add 1.5 mL of *ammonia R*. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution Dissolve 3.5 g of *dipotassium hydrogen phosphate R* in 1000 mL of *water for chromatography R* and adjust to pH 7.0 with *phosphoric acid R*.

Test solution Dissolve 20 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) Dissolve 4 mg of *amorolfine for system suitability CRS* (containing impurities D, E, I and J) in mobile phase A and dilute to 5 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 4 mg of *amorolfine for peak identification CRS* (containing impurity M) in mobile phase A and dilute to 5 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped amidohexadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, buffer solution, *methanol R2* (5:35:60 *V/V/V*);

— *mobile phase B*: buffer solution, *acetonitrile R1*, *methanol R2* (10:30:60 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 25	90 → 0	10 → 100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 214 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *amorolfine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities D, E, I and J; use the chromatogram supplied with *amorolfine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurity M (peaks 1 and 2).

Relative retention With reference to amorolfine (retention time = about 15 min): impurity M (peak 1) = about 0.56; impurity M (peak 2) = about 0.60; impurity D = about 0.85; impurity J = about 0.97; impurity I = about 1.05; impurity E (peak 1) = about 1.14; impurity E (peak 2) = about 1.17.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity J and amorolfine in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 20 for the principal peak in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— for each impurity, use the concentration of amorolfine hydrochloride in reference solution (b).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *impurity E*: maximum 0.2 per cent for the sum of the areas of the 2 peaks;

— *impurity I*: maximum 0.15 per cent;

— *impurity M* : maximum 0.15 per cent for each peak;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 10.0 mL of *0.01 M hydrochloric acid* and 40 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

www.webofpharma.com

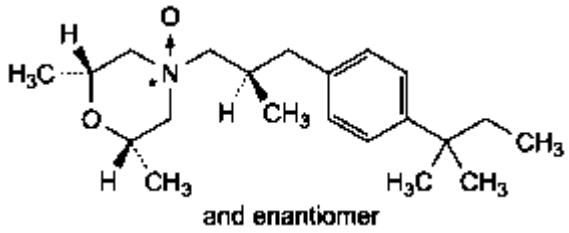
https://thuocngocanh.com/

1 mL of *0.1 M sodium hydroxide* is equivalent to 35.40 mg of $C_{21}H_{36}ClNO$.

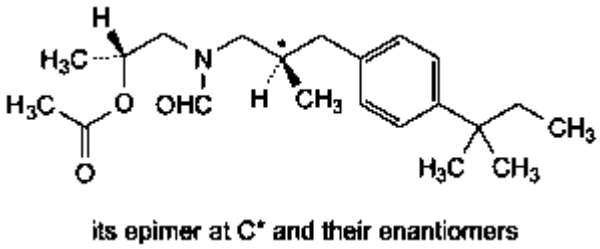
IMPURITIES

Specified impurities D, E, I, M.

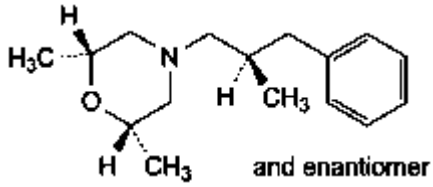
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, F, G, H, J, K, L, O.



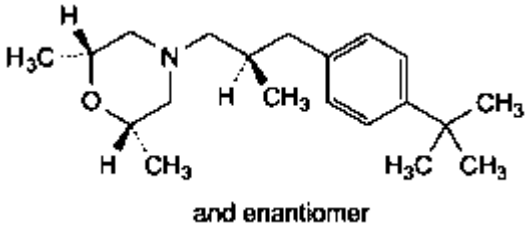
A. (2*RS*,4Ξ,6*SR*)-2,6-dimethyl-4-[(2*RS*)-2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]propyl]morpholine 4-oxide,



B. mixture of (2*RS*)-1-[*N*-[(2*R*)-2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]propyl]formamido]propan-2-yl acetate and (2*RS*)-1-[*N*-[(2*S*)-2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]propyl]formamido]propan-2-yl acetate,



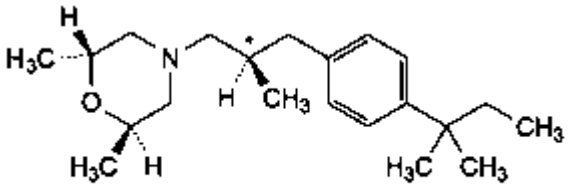
C. (2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-2-methyl-3-phenylpropyl]morpholine,



D. (2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-3-(4-*tert*-butylphenyl)-2-methylpropyl]morpholine,

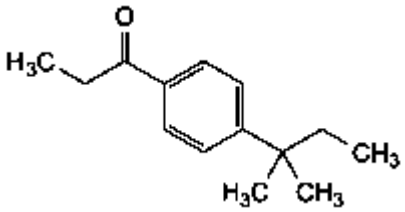
www.webofpharma.com

https://thuocngocanh.com/

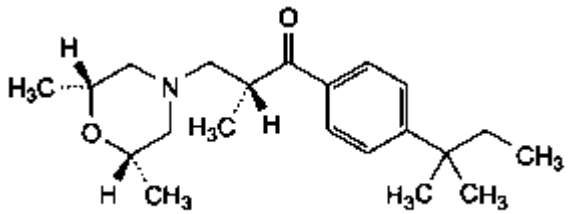


its epimer at C* and their enantiomers

E. mixture of (2*RS*,6*RS*)-2,6-dimethyl-4-[(2*R*)-2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]propyl]morpholine and (2*RS*,6*RS*)-2,6-dimethyl-4-[(2*S*)-2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]propyl]morpholine,

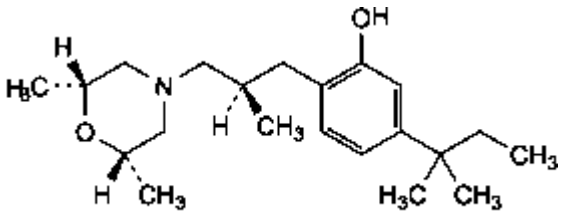


F. 1-[4-(2-methylbutan-2-yl)phenyl]propan-1-one,



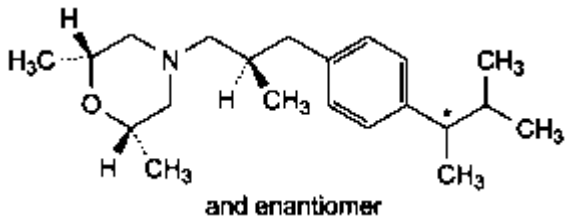
and enantiomer

G. (2*RS*)-3-[(2*RS*,6*SR*)-2,6-dimethylmorpholin-4-yl]-1-[4-(2-methylbutan-2-yl)phenyl]-2-methylpropan-1-one,



and enantiomer

H. 2-[(2*RS*)-3-[(2*RS*,6*SR*)-2,6-dimethylmorpholin-4-yl]-2-methylpropyl]-5-(2-methylbutan-2-yl)phenol,

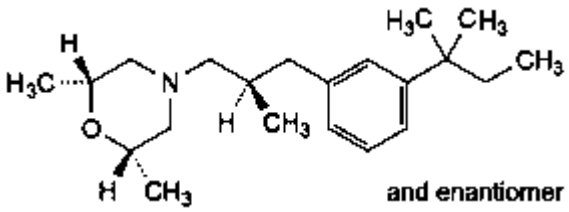


and enantiomer

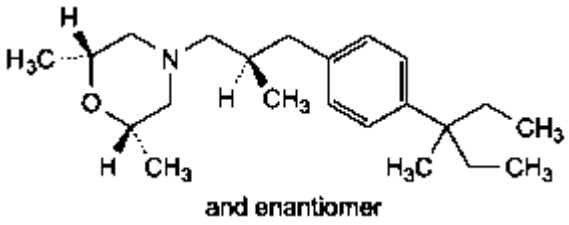
I. (2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-2-methyl-3-[4-[(2Ξ)-3-methylbutan-2-yl]phenyl]propyl]morpholine,

www.webofpharma.com

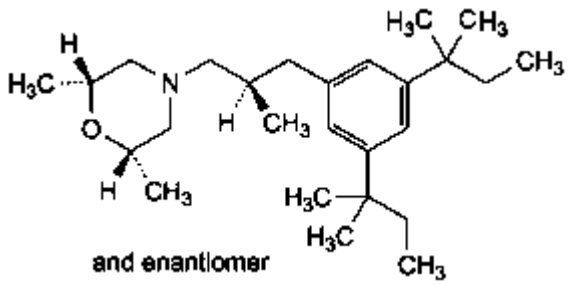
https://thuocngocanh.com/



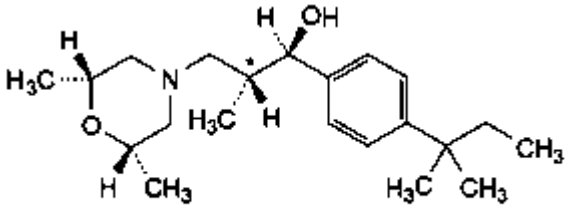
J. (2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-2-methyl-3-[3-(2-methylbutan-2-yl)phenyl]propyl]morpholine,



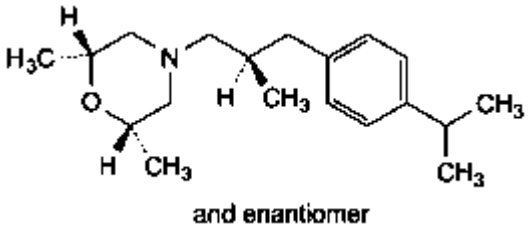
K. (2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-2-methyl-3-[4-(3-methylpentan-3-yl)phenyl]propyl]morpholine,



L. (2*RS*,6*SR*)-4-[(2*RS*)-3-[3,5-bis(2-methylbutan-2-yl)phenyl]-2-methylpropyl]-2,6-dimethylmorpholine,



M. mixture of (1*RS*,2*RS*)-3-[(2*RS*,6*SR*)-2,6-dimethylmorpholin-4-yl]-2-methyl-1-[4-(2-methylbutan-2-yl)phenyl]propan-1-ol and (1*RS*,2*SR*)-3-[(2*RS*,6*SR*)-2,6-dimethylmorpholin-4-yl]-2-methyl-1-[4-(2-methylbutan-2-yl)phenyl]propan-1-ol,



O. (2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-2-methyl-3-[4-(propan-2-yl)phenyl]propyl]morpholine.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products
Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amoxicillin Capsules

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Amoxicillin Capsules contain Amoxicillin Trihydrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of amoxicillin, $C_{16}H_{19}N_3O_5S$

92.5 to 110.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing the equivalent of 0.5 g of amoxicillin with 5 mL of *water* for 5 minutes, filter, wash the residue first with *absolute ethanol* and then with *ether* and dry at a pressure not exceeding 0.7 kPa for 1 hour. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of amoxicillin trihydrate *(RS 011)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the residue in sufficient *sodium hydrogen carbonate solution* to produce a solution containing the equivalent of 0.25% w/v of amoxicillin.

(2) 0.25% w/v of *amoxicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

(3) 0.25% w/v of each of *amoxicillin trihydrate BPCRS* and *ampicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel silanised plate* (Merck silanised silica gel 60 F_{254s} (RP-18) plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 80 mL of mobile phase A to a quantity of the mixed capsule contents containing the equivalent of 0.15 g of amoxicillin and shake for 15 minutes. Mix with the aid of ultrasound for 1 minute, add sufficient mobile phase A to produce 100 mL, mix and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.
(3) 0.0004% w/v of *cefadroxil BPCRS* and 0.003% w/v of *amoxicillin trihydrate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *acetonitrile* and 99 volumes of a pH 5.0 buffer solution prepared in the following manner. To 250 mL of 0.2M *potassium dihydrogen orthophosphate* add 2M *sodium hydroxide* until the pH reaches 5.0 and add sufficient *water* to produce 1000 mL.

Mobile phase B 20 volumes of *acetonitrile* and 80 volumes of the pH 5.0 buffer solution.

Equilibrate the column with a mobile phase ratio A:B of 92:8. Inject solutions (1) and (2) and start the elution isocratically with the chosen mobile phase. Immediately after elution of the amoxicillin peak start a linear gradient elution to reach a mobile phase ratio A:B of 0:100 over a period of 25 minutes. Continue the chromatography with mobile phase B for 15 minutes then equilibrate the column for 15 minutes with the mobile phase chosen originally. Inject mobile phase A and use the same elution gradient to obtain a blank.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to amoxicillin and cefadroxil is at least 2.0. If necessary, adjust the composition of the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of not more than one *secondary peak* is greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 80 mL of mobile phase A to a quantity of the mixed contents of 20 capsules containing the equivalent of 60 mg of amoxicillin and shake for 15 minutes. Mix with the aid of ultrasound for 1 minute, add sufficient mobile phase A to produce 100 mL, mix and filter (Whatman GF/C filter paper is suitable).

(2) 0.070% w/v of *amoxicillin trihydrate BPCRS* in mobile phase A.

(3) 0.0004% w/v of *cefadroxil BPCRS* and 0.003% w/v of *amoxicillin trihydrate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

8 volumes of mobile phase B and 92 volumes of mobile phase A.

Mobile phase A 1 volume of *acetonitrile* and 99 volumes of a 25% v/v solution of 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide*.

Mobile phase B 20 volumes of *acetonitrile* and 80 volumes of a 25% v/v solution of 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to amoxicillin and cefadroxil is at least 2.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{19}N_3O_5S$ in the capsules from the chromatograms obtained and from the declared content of $C_{16}H_{19}N_3O_5S$ in *amoxicillin trihydrate BPCRS*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of amoxicillin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amoxicillin Injection

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Amoxicillin Injection is a sterile solution of Amoxicillin Sodium in Water for Injections. It is prepared by dissolving Amoxicillin Sodium for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Amoxicillin Injection should be used immediately after preparation.

AMOXICILLIN SODIUM FOR INJECTION

DEFINITION

Amoxicillin Sodium for Injection is a sterile material consisting of Amoxicillin Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of amoxicillin, $C_{16}H_{19}N_3O_5S$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of amoxicillin sodium *(RS 010)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of a sealed container in sufficient *sodium hydrogen carbonate solution* to produce a solution containing the equivalent of 0.25% w/v of amoxicillin.

(2) 0.25% w/v of *amoxicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

(3) 0.25% w/v of each of *amoxicillin trihydrate BPCRS* and *ampicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a *TLC silica gel F_{254} silanised plate* (Merck silanised silica gel 60 F_{254s} (RP-18) plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose it to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

C. Yields reaction B characteristic of *sodium salts*, Appendix VI.

TESTS

Alkalinity

pH of a solution containing the equivalent of 10% w/v of amoxicillin, 8.0 to 10.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 80 mL of mobile phase A to a quantity of the contents of a sealed container containing the equivalent of 0.15 g of amoxicillin and shake for 15 minutes. Mix with the aid of ultrasound for 1 minute, add sufficient mobile phase A to produce 100 mL, mix and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) Add 1 mL of *water* to 0.2 g of *amoxicillin trihydrate BPCRS*, shake and add, dropwise, *dilute sodium hydroxide solution* to obtain a solution. (The pH of the solution is about 8.5.) Store the solution at room temperature for 4 hours and dilute 0.5 mL to 50 mL with mobile phase A.

(4) 0.0004% w/v of *cefadroxil BPCRS* and 0.003% w/v of *amoxicillin trihydrate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

Mobile phase A Mix 1 volume of *acetonitrile* and 99 volumes of a pH 5.0 buffer solution prepared in the following manner. To 250 mL of 0.2 M *potassium dihydrogen orthophosphate* add 2M *sodium hydroxide* until the pH reaches 5.0 and add sufficient *water* to produce 1000 mL.

Mobile phase B Mix 20 volumes of *acetonitrile* and 80 volumes of the pH 5.0 buffer solution.

Equilibrate the column with a mobile phase ratio A:B of 92:8. Inject solutions (1) and (2) and start the elution isocratically with the chosen mobile phase. Immediately after elution of the amoxicillin peak start a linear gradient elution to reach a mobile phase ratio A:B of 1:100 over a period of 25 minutes. Continue the chromatography with mobile phase B for 15 minutes then equilibrate the column for 15 minutes with the mobile phase chosen originally. Inject mobile phase A and use the same elution gradient to obtain a blank.

Inject solution (3). The three main peaks eluted after the principal peak correspond to amoxicillin diketopiperazine, amoxicillin dimer and amoxicillin trimer. The retention times of these peaks relative to that of the principal peak are about 3.4, 4.1 and 4.5 respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to amoxicillin and cefadroxil is at least 2.0. If necessary, adjust the composition of the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to amoxicillin dimer is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the sum of the areas of all the *secondary peaks* is not greater than 9 times the area of the principal peak in the chromatogram obtained with solution (2) (9%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Water

Not more than 4.0% w/w, Appendix IX C. Use 0.3 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg per mL of amoxicillin (solution A). The endotoxin limit concentration of solution A is 2.5 IU of endotoxin per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 80 mL of mobile phase A to a quantity of the mixed contents of the 10 containers containing the equivalent of 60 mg of amoxicillin and shake for 15 minutes. Mix with the aid of ultrasound for 1 minute, add sufficient mobile phase A to produce 100 mL, mix and filter (Whatman GF/C filter paper is suitable).

(2) 0.070% w/v of *amoxicillin trihydrate BPCRS* in mobile phase A.

(3) 0.0004% w/v of *cefadroxil BPCRS* and 0.003% w/v of *amoxicillin trihydrate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

A mixture of 8 volumes of mobile phase B and 92 volumes of mobile phase A.

Mobile phase A Mix 1 volume of *acetonitrile* and 99 volumes of a 25% v/v solution of 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide*.

Mobile phase B Mix 20 volumes of *acetonitrile* and 80 volumes of a 25% v/v solution of 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to amoxicillin and cefadroxil is at least 2.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{19}N_3O_5S$ in a container of average content weight from the chromatograms obtained and from the declared content of $C_{16}H_{19}N_3O_5S$ in *amoxicillin trihydrate BPCRS*.

LABELLING

The label of the sealed container states the quantity of Amoxicillin Sodium contained in it in terms of the equivalent amount of amoxicillin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amoxicillin Oral Suspension

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Amoxicillin Oral Suspension is a suspension of Amoxicillin Trihydrate in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of Water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of amoxicillin, $C_{16}H_{19}N_3O_5S$

When freshly constituted not more than 120.0% of the stated amount. When stored at the temperature and for the period stated on the label during which the Oral Suspension may be expected to be satisfactory for use, not less than 80.0% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the oral suspension with sufficient *sodium hydrogen carbonate solution* to produce a solution containing the equivalent of 0.25% w/v of amoxicillin.
(2) 0.25% w/v of *amoxicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.
(3) 0.25% w/v of each of *amoxicillin trihydrate BPCRS* and *ampicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel silanised plate* (Merck silanised silica gel 60 F_{254s} (RP-18) plates are suitable).
(b) Use the mobile phase described below.
(c) Apply 1 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, allow it to dry in air, expose it to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 4.0 to 7.0, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral suspension containing the equivalent of 60 mg of amoxicillin with sufficient mobile phase A to produce 100 mL, mix and filter (Whatman GF/C filter paper is suitable).
(2) 0.070% w/v of *amoxicillin trihydrate BPCRS* in mobile phase A.
(3) 0.0004% w/v of *cefadroxil BPCRS* and 0.003% w/v of *amoxicillin trihydrate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

8 volumes of mobile phase B and 92 volumes of mobile phase A.

Mobile phase A Mix 1 volume of *acetonitrile* and 99 volumes of a 25% v/v solution of 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide*.

Mobile phase B Mix 20 volumes of *acetonitrile* and 80 volumes of a 25% v/v solution of 0.2M *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to amoxicillin and cefadroxil is at least 2.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{16}H_{19}N_3O_5S$, weight in volume, using the declared content of $C_{16}H_{19}N_3O_5S$ in *amoxicillin trihydrate BPCRS*.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The Oral Suspension should be kept at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of amoxicillin.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

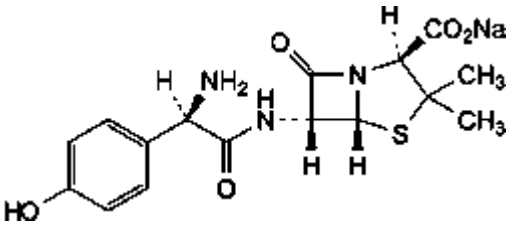
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amoxicillin Sodium

General Notices

(Ph. Eur. monograph 0577)



$C_{16}H_{18}N_3NaO_5S$ 387.4 *34642-77-8*

Action and use

Penicillin antibacterial.

Preparations

Amoxicillin Injection

Co-amoxiclav Injection

Ph Eur

DEFINITION

Sodium (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

89.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic, powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Very soluble in water, sparingly soluble in anhydrous ethanol, very slightly soluble in acetone.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 0.250 g in 5 mL of water R, add 0.5 mL of dilute acetic acid R, swirl and allow to stand for 10 min in iced water. Filter the crystals and wash with 2-3 mL of a mixture of 1 volume of water R and 9 volumes of acetone R, then dry in an oven at 60 °C for 30 min.

Comparison amoxicillin trihydrate CRS.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of sodium hydrogen carbonate solution R.

Reference solution (a) Dissolve 25 mg of amoxicillin trihydrate CRS in 10 mL of sodium hydrogen carbonate solution R.

Reference solution (b) Dissolve 25 mg of amoxicillin trihydrate CRS and 25 mg of ampicillin trihydrate CRS in 10 mL of sodium hydrogen carbonate solution R.

Plate TLC silanised silica gel plate R.

Mobile phase Mix 10 volumes of acetone R and 90 volumes of a 154 g/L solution of ammonium acetate R previously adjusted to pH 5.0 with glacial acetic acid R.

Application 1 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and about 15 mm in diameter. Moisten with 0.05 mL of water R and add 2 mL of sulfuric acid-formaldehyde reagent R. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube in a water-bath for 1 min; a dark yellow colour develops.

D. It gives reaction (a) of sodium (2.3.1).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1), it may show an initial, but transient, pink colour, and after 5 min, its absorbance (2.2.25) at 430 nm is not greater than 0.20.

Dissolve 1.0 g in *water R* and dilute to 10.0 mL with the same solvent. Examine immediately after dissolution.

pH (2.2.3)

8.0 to 10.0.

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 240 to + 290 (anhydrous substance).

Dissolve 62.5 mg in a 4 g/L solution of *potassium hydrogen phthalate R* and dilute to 25.0 mL with the same solution.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 30.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Test solution (b) Dissolve 30.0 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A. *Prepare immediately before use*.

Reference solution (a) Dissolve 30.0 mg of *amoxicillin trihydrate CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dissolve 4.0 mg of *cefadroxil CRS* in mobile phase A and dilute to 50 mL with mobile phase A. To 5.0 mL of this solution add 5.0 mL of reference solution (a) and dilute to 100 mL with mobile phase A.

Reference solution (c) Dilute 2.0 mL of reference solution (a) to 20.0 mL with mobile phase A. Dilute 5.0 mL of this solution to 20.0 mL with mobile phase A.

Reference solution (d) To 0.20 g of *amoxicillin trihydrate R* add 1.0 mL of *water R*. Shake and add dropwise *dilute sodium hydroxide solution R* to obtain a solution. The pH of the solution is about 8.5. Store the solution at room temperature for 4 h. Dilute 0.5 mL of this solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: mix 1 volume of *acetonitrile R* and 99 volumes of a 25 per cent *V/V* solution of *0.2 M potassium dihydrogen phosphate R* adjusted to pH 5.0 with *dilute sodium hydroxide solution R*;

— *mobile phase B*: mix 20 volumes of *acetonitrile R* and 80 volumes of a 25 per cent *V/V* solution of *0.2 M potassium dihydrogen phosphate R* adjusted to pH 5.0 with *dilute sodium hydroxide solution R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	92	8
t_R - (t_R + 25)	92 → 0	8 → 100
(t_R + 25) - (t_R + 40)	0	100
(t_R + 40) - (t_R + 55)	92	8

t_R = retention time of amoxicillin determined with reference solution (c)

If the mobile phase has been adjusted to achieve the required resolution, the adjusted composition will apply at time zero in the gradient and in the assay.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 50 µL of reference solutions (b) and (c) with isocratic elution at the initial mobile phase composition and 50 µL of test solution (b) and reference solution (d) according to the elution gradient described under Mobile phase; inject mobile phase A as a blank according to the elution gradient described under Mobile phase.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the 3 principal peaks eluted after the main peak corresponding to impurity C, amoxicillin dimer (impurity J; *n* = 1) and amoxicillin trimer (impurity J; *n* = 2).

Relative retention With reference to amoxicillin: impurity C = about 3.4; impurity J (*n* = 1) = about 4.1; impurity J (*n* = 2) = about 4.5.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to amoxicillin and cefadroxil; if necessary, adjust the ratio A:B of the mobile phase.

Limits:

— *impurity J* (*n* = 1): not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3 per cent);

— *any other impurity*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (2 per cent);

— *total*: not more than 9 times the area of the principal peak in the chromatogram obtained with reference solution (c) (9 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

***N*,*N*-Dimethylaniline** (*2.4.26, Method A or B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.8 per cent *m/m*.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.400 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.25 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Initial composition of the mixture of mobile phases A and B, adjusted where applicable.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

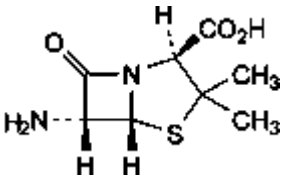
— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of amoxicillin sodium by multiplying the percentage content of amoxicillin by 1.060.

STORAGE

In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

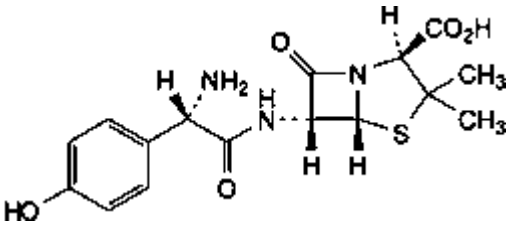
IMPURITIES



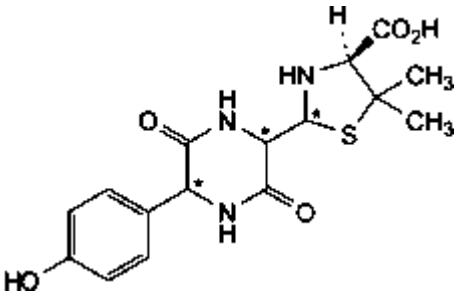
A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),

www.webofpharma.com

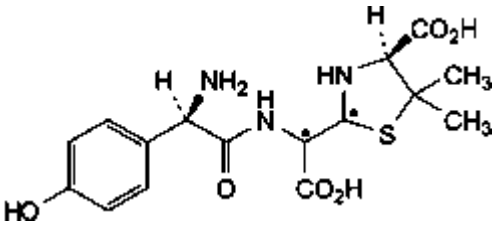
https://thuocngocanh.com/



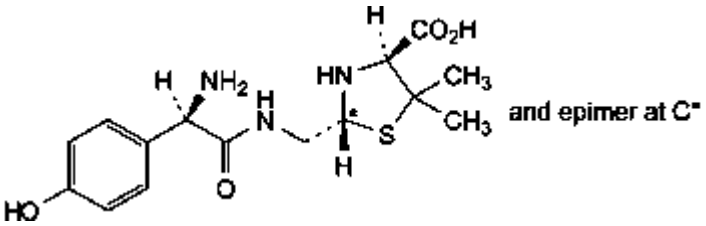
B. (2*S*,5*R*,6*R*)-6-[[(2*S*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-amoxicillin),



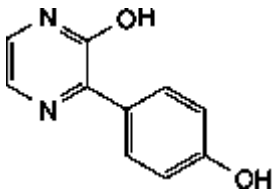
C. (4*S*)-2-[5-(4-hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5,5-dimethylthiazolidine-4-carboxylic acid (amoxicillin diketopiperazines),



D. (4*S*)-2-[[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of amoxicillin),



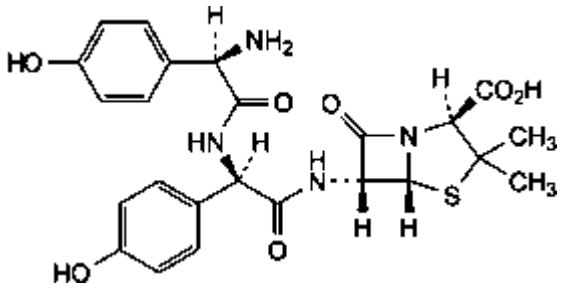
E. (2*RS*,4*S*)-2-[[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of amoxicillin),



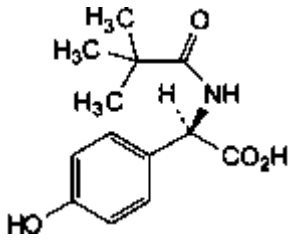
F. 3-(4-hydroxyphenyl)pyrazin-2-ol,

www.webofpharma.com

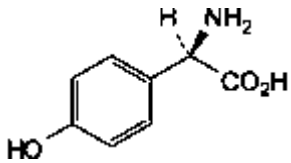
https://thuocngocanh.com/



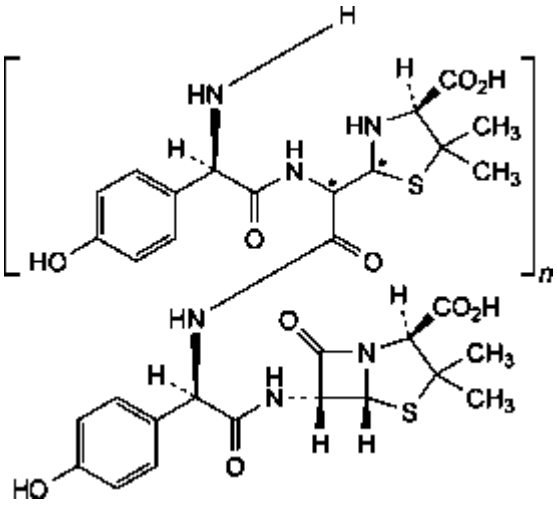
G. (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane2-carboxylic acid (D-(4-hydroxyphenyl)glycylamoxicillin),



H. (2*R*)-2-[(2,2-dimethylpropanoyl)amino]-2-(4-hydroxyphenyl)acetic acid,



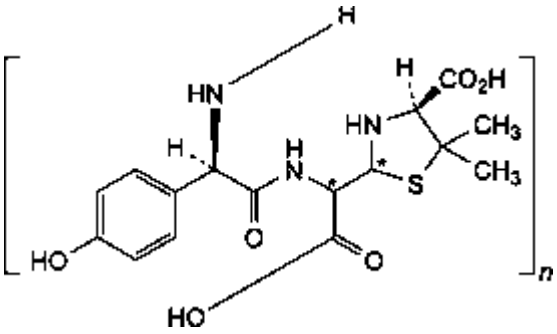
I. (2*R*)-2-amino-2-(4-hydroxyphenyl)acetic acid,



J. co-oligomers of amoxicillin and penicilloic acids of amoxicillin,

www.webofpharma.com

https://thuocngocanh.com/



K. oligomers of penicilloic acids of amoxicillin.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

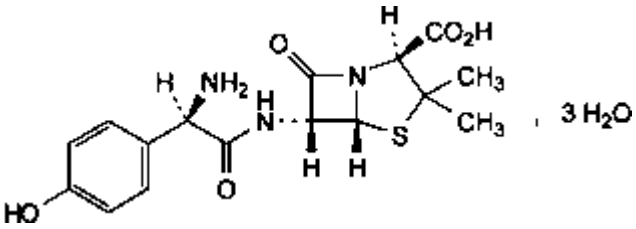
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amoxicillin Trihydrate

General Notices

(Ph. Eur. monograph 0260)



$C_{16}H_{19}N_3O_5S,3H_2O$ 419.4 *61336-70-7*

Action and use

Penicillin antibacterial.

Preparations

Amoxicillin Capsules

Amoxicillin Oral Suspension

Co-amoxiclav Oral Suspension

Co-amoxiclav Tablets

Co-amoxiclav Dispersible Tablets

Ph Eur

DEFINITION

(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *amoxicillin trihydrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of *sodium hydrogen carbonate solution R*.

Reference solution (a) Dissolve 25 mg of *amoxicillin trihydrate CRS* in 10 mL of *sodium hydrogen carbonate solution R*.

Reference solution (b) Dissolve 25 mg of *amoxicillin trihydrate CRS* and 25 mg of *ampicillin trihydrate CRS* in 10 mL of *sodium hydrogen carbonate solution R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 10 volumes of *acetone R* and 90 volumes of a 154 g/L solution of *ammonium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and about 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube in a

www.webofpharma.com

https://thuocngocanh.com/

water-bath for 1 min; a dark yellow colour develops.

TESTS

Solution S

With the aid of ultrasound or gentle heating, dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

pH (2.2.3)

3.5 to 5.5 for solution S.

Specific optical rotation (2.2.7)

+ 290 to + 315 (anhydrous substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Buffer solution pH 5.0 To 250 mL of *0.2 M potassium dihydrogen phosphate R* add *dilute sodium hydroxide solution R* to pH 5.0 and dilute to 1000.0 mL with *water R*.

Test solution (a) Dissolve 30.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Test solution (b) Dissolve 30.0 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A. *Prepare immediately before use.*

Reference solution (a) Dissolve 30.0 mg of *amoxicillin trihydrate CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dissolve 4.0 mg of *cefadroxil CRS* in mobile phase A and dilute to 50 mL with mobile phase A. To 5.0 mL of this solution add 5.0 mL of reference solution (a) and dilute to 100 mL with mobile phase A.

Reference solution (c) Dilute 2.0 mL of reference solution (a) to 20.0 mL with mobile phase A. Dilute 5.0 mL of this solution to 20.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, buffer solution pH 5.0 (1:99 *V/V*);

— *mobile phase B*: *acetonitrile R*, buffer solution pH 5.0 (20:80 *V/V*);

www.webofpharma.com

https://thuvienthuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	92	8
t_R - (t_R + 25)	92 → 0	8 → 100
(t_R + 25) - (t_R + 40)	0	100
(t_R + 40) - (t_R + 55)	92	8

t_R = retention time of amoxicillin determined with reference solution (c)

If the mobile phase composition has been adjusted to achieve the required resolution, the adjusted composition will apply at time zero in the gradient and in the assay.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 50 µL of reference solutions (b) and (c) with isocratic elution at the initial mobile phase composition and 50 µL of test solution (b) according to the elution gradient described under Mobile phase; inject mobile phase A as a blank according to the elution gradient described under Mobile phase.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to amoxicillin and cefadroxil; if necessary, adjust the ratio A:B of the mobile phase.

Limit:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method A or B*)

Maximum 20 ppm.

Water (*2.5.12*)

11.5 per cent to 14.5 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Initial composition of the mixture of mobile phases A and B, adjusted where applicable.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

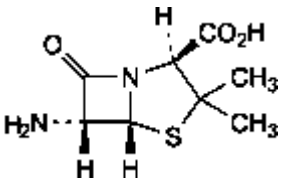
— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{16}H_{19}N_3O_5S$ taking into account the assigned content of *amoxicillin trihydrate CRS*.

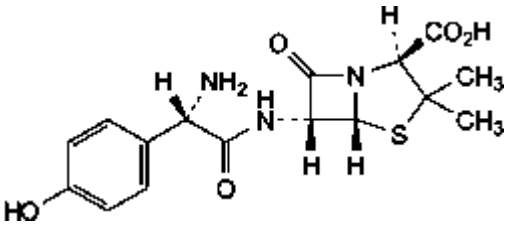
STORAGE

In an airtight container.

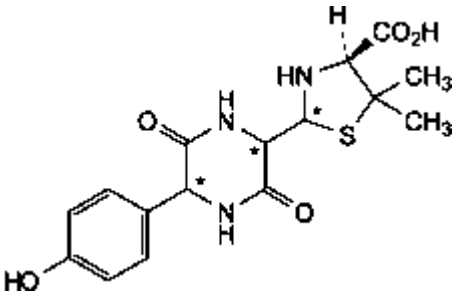
IMPURITIES



A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



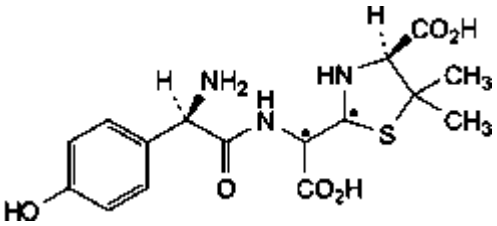
B. (2*S*,5*R*,6*R*)-6-[[(2*S*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-amoxicillin),



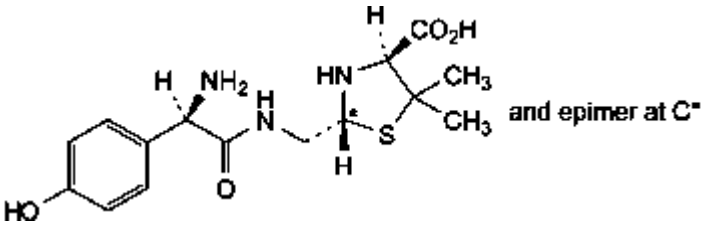
C. (4*S*)-2-[5-(4-hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5,5-dimethylthiazolidine-4-carboxylic acid (amoxicillin diketopiperazines),

www.webofpharma.com

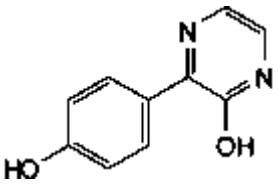
https://thuocngocanh.com/



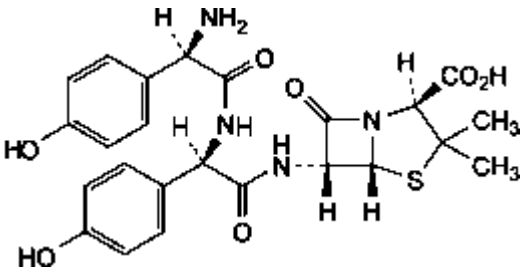
D. (4*S*)-2-[[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of amoxicillin),



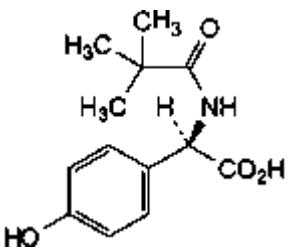
E. (2*RS*,4*S*)-2-[[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of amoxicillin),



F. 3-(4-hydroxyphenyl)pyrazin-2-ol,



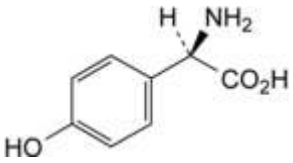
G. (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-2-(4-hydroxy-phenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (D-(4-hydroxyphenyl)glycylamoxicillin),



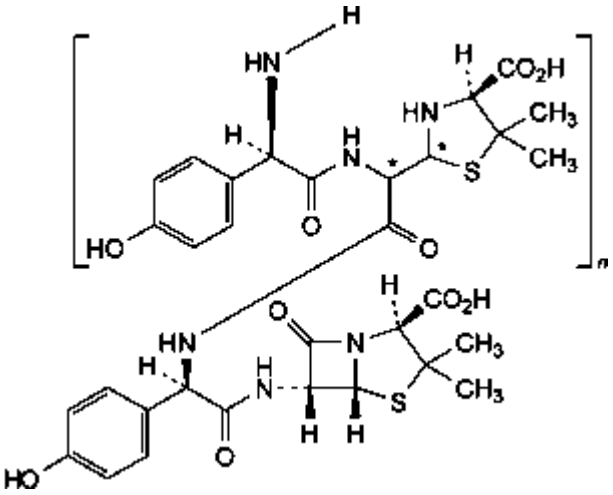
H. (2*R*)-2-[(2,2-dimethylpropanoyl)amino]-2-(4-hydroxyphenyl)acetic acid,

www.webofpharma.com

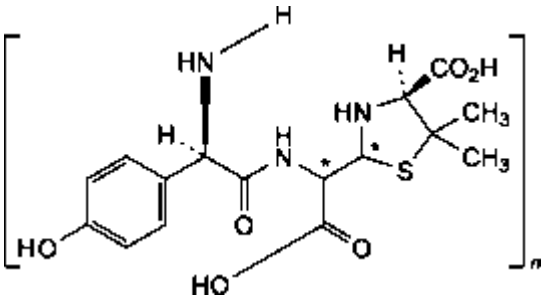
https://thuocngocanh.com/



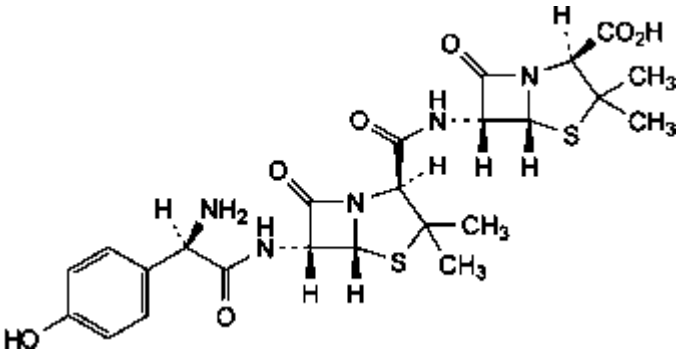
I. (2*R*)-2-amino-2-(4-hydroxyphenyl)acetic acid,



J. co-oligomers of amoxicillin and of penicilloic acids of amoxicillin,



K. oligomers of penicilloic acids of amoxicillin,



L. (2*S*,5*R*,6*R*)-6-[[(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-APA amoxicillin amide).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

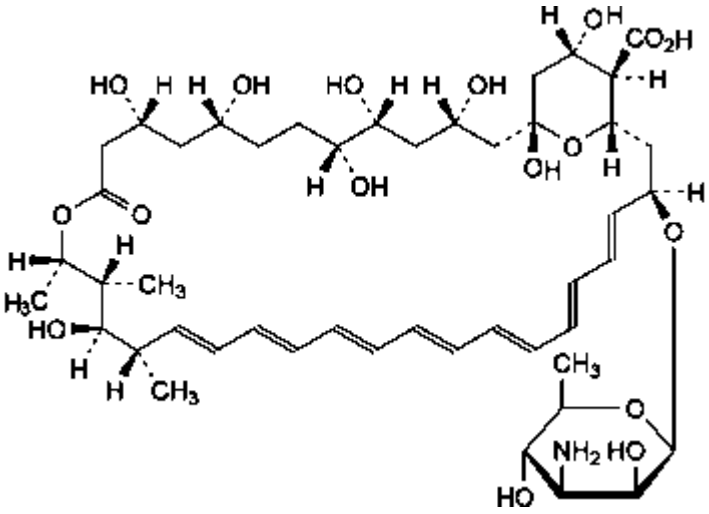
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amphotericin

General Notices

(Amphotericin B, Ph. Eur. monograph 1292)



$C_{47}H_{73}NO_{17}$ 924 *1397-89-3*

Action and use

Antifungal.

Preparation

Amphotericin for Infusion

Ph Eur

DEFINITION

Mixture of antifungal polyenes produced by the growth of certain strains of *Streptomyces nodosus* or obtained by any other means. It consists mainly of amphotericin B which is (1*R*,3*S*,5*R*,6*R*,9*R*,11*R*,15*S*,16*R*,17*R*,18*S*,19*E*,21*E*,23*E*,-25*E*,27*E*,29*E*,31*E*,33*R*,35*S*,36*R*,37*S*)-33-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxa-bicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid.

Content

Minimum 750 IU/mg (dried substance).

CHARACTERS

https://thuocngocanh.com/

Appearance

Yellow or orange, hygroscopic powder.

Solubility

Practically insoluble in water, soluble in dimethyl sulfoxide and in propylene glycol, slightly soluble in dimethylformamide, very slightly soluble in methanol, practically insoluble in ethanol (96 per cent).

It is sensitive to light in dilute solutions.

IDENTIFICATION

First identification: B, D.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25 mg in 5 mL of *dimethyl sulfoxide R* and dilute to 50 mL with *methanol R*. Dilute 2 mL of the solution to 200 mL with *methanol R*.

Spectral range 300-450 nm.

Absorption maxima At 362 nm, 381 nm and 405 nm.

Absorbance ratios:

— A_{362}/A_{381} = 0.57 to 0.61;

— A_{381}/A_{405} = 0.87 to 0.93.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *amphotericin B CRS*.

If the spectra obtained show differences, dry the substance to be examined and reference substance at 60 °C at a pressure not exceeding 0.7 kPa for 1 h and record new spectra.

C. To 1 mL of a 0.5 g/L solution in *dimethyl sulfoxide R*, add 5 mL of *phosphoric acid R* to form a lower layer, avoiding mixing the 2 liquids. A blue ring is immediately produced at the junction of the liquids. Mix, an intense blue colour is produced. Add 15 mL of *water R* and mix; the solution becomes pale yellow.

D. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution at 383 nm is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light and use within 24 h of preparation, except for reference solution (c) which should be injected immediately after its preparation.*

Solvent mixture 10 g/L solution of *ammonium acetate R*, *N-methylpyrrolidone R*, *methanol R* (1:1:2 *V/V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in 15 mL of *N-methylpyrrolidone R* and within 2 h dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 20.0 mg of *amphotericin B CRS* in 15 mL of *N-methylpyrrolidone R* and within 2 h dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 25.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 20.0 mg of *nystatin CRS* in 15 mL of *N-methylpyrrolidone R* and within 2 h dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 25.0 mL with reference solution (a). Dilute 2.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (d) In order to prepare impurities B and C, dissolve 10 mg of the substance to be examined in 5 mL of *N-methylpyrrolidone R* and within 2 h add 35 mL of a mixture of 1 volume of *methanol R* and 4 volumes of *anhydrous ethanol R*. Add 0.10 mL of *dilute hydrochloric acid R*, mix and incubate at 25 °C for 2.5 h. Add 10 mL of 10 g/L solution of *ammonium acetate R* and mix.

Reference solution (e) Dissolve 4 mg of *amphotericin B for peak identification CRS* (containing impurities A and B) in 5 mL of *N-methylpyrrolidone R* and within 2 h dilute to 50 mL with the solvent mixture.

Blank solution The solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 20 °C.

Mobile phase:

— *mobile phase A*: mix 1 volume of *methanol R*, 3 volumes of *acetonitrile R* and 6 volumes of a 4.2 g/L solution of *citric acid monohydrate R* previously adjusted to pH 4.7 using *concentrated ammonia R*;

— *mobile phase B*: mix 12 volumes of *methanol R*, 20 volumes of a 4.2 g/L solution of *citric acid monohydrate R* previously adjusted to pH 3.9 using *concentrated ammonia R* and 68 volumes of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0

www.webofpharma.com

https://thuvienthuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
3 - 23	100 → 70	0 → 30
23 - 33	70 → 0	30 → 100
33 - 40	0	100

Flow rate 0.8 mL/min.

Detection Spectrophotometer:

— at 303 nm: detection of tetraenes;

— at 383 nm: detection of heptaenes.

Injection 20 µL of the test solution and reference solutions (b), (c), (d) and (e).

Identification of impurities Use the chromatograms supplied with *amphotericin B for peak identification CRS* and the chromatograms obtained with reference solution (e) to identify the peaks due to impurities A and B.

Relative retention With reference to amphotericin B (retention time = about 16 min): impurity B = about 0.75; impurity A = about 0.8; nystatin = about 0.85.

System suitability at 383 nm Reference solution (d):

— *resolution*: minimum 1.5 between the 2 peaks presenting a relative retention of about 0.7.

Limits:

— *impurity A at 303 nm*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (5.0 per cent); if intended for use in the manufacture of parenteral preparations: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent);

— *any other impurity at 303 nm*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *impurity B at 383 nm*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (4.0 per cent);

— *any other impurity at 383 nm*: for each impurity, not more than 2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *total at 303 and 383 nm*: maximum 15.0 per cent;

— *disregard limit at 303 nm*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit at 383 nm*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 60 °C at a pressure not exceeding 0.7 kPa.

Sulfated ash (2.4.14)

Maximum 3.0 per cent, determined on 1.0 g; if intended for use in the manufacture of parenteral preparations: maximum 0.5 per cent.

Bacterial endotoxins (2.6.14)

Less than 1.0 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Protect all solutions from light throughout the assay Dissolve 25.0 mg in *dimethyl sulfoxide R* and dilute, with shaking, to 25.0 mL with the same solvent. Under constant stirring of this stock solution, dilute with *dimethyl sulfoxide R* to obtain solutions of appropriate concentrations (the following concentrations have been found suitable: 44.4, 66.7 and 100 IU/mL). Prepare final solutions by diluting 1:20 with 0.2 M phosphate buffer solution pH 10.5 so that they all contain 5 per cent *V/V* of dimethyl sulfoxide. Prepare the reference and the test solutions simultaneously. Carry out the microbiological assay of antibiotics (2.7.2). Use *amphotericin B for microbiological assay CRS* as the chemical reference substance.

STORAGE

Protected from light, at a temperature of 2 °C to 8 °C in an airtight container. If the substance is sterile, store in a sterile, tamper-evident container.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

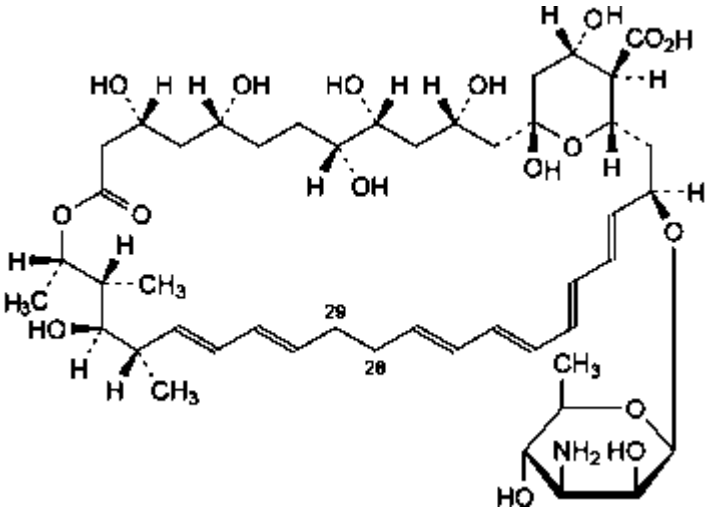
IMPURITIES

Specified impurities *A, B.*

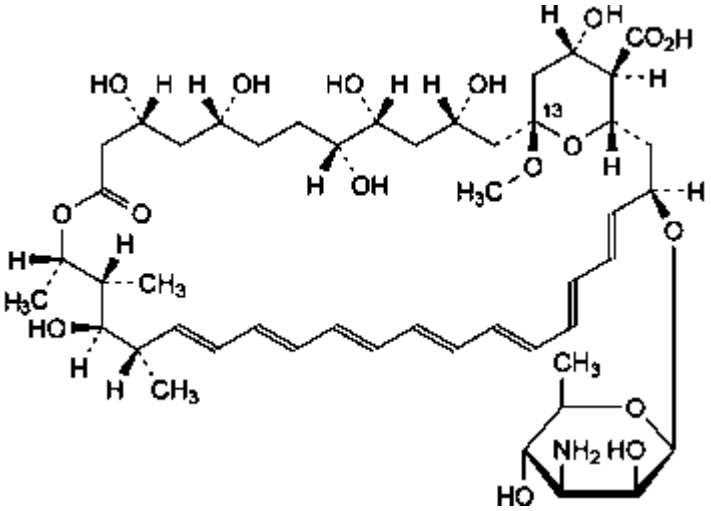
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*

www.webofpharma.com

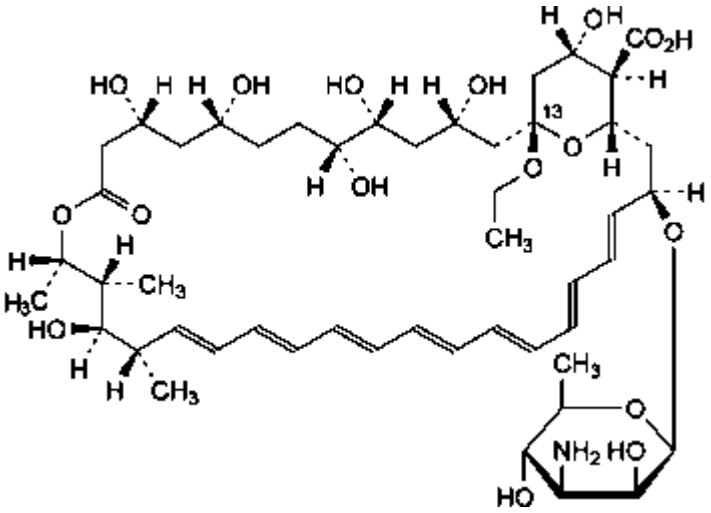
https://thuocngocanh.com/



A. amphotericin A (28,29-dihydro-amphotericin B),



B. amphotericin X1 (13-*O*-methyl-amphotericin B),



C. amphotericin X2 (13-*O*-ethyl-amphotericin B).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products
Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Amphotericin for Infusion

General Notices

Amphotericin for Infusion from different manufacturers, whilst complying with the requirements of the monograph, is not interchangeable unless otherwise justified and authorised.

This monograph does not apply to formulations where Amphotericin is encapsulated in liposomes.

Action and use

Antifungal.

DEFINITION

Amphotericin for Infusion is a sterile material consisting of Amphotericin as a sodium deoxycholate complex, with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

IDENTIFICATION

A. Dissolve a quantity of the contents of a sealed container containing the equivalent of 25 mg of amphotericin B in *methanol* and add sufficient *methanol* to produce 50 mL.Dilute 0.5 mL of this solution to 50 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 300 to 450 nm exhibits three maxima, at 362, 381 and 405 nm. The ratio of the *absorbance* at the maximum at 362 nm to that at the maximum at 381 nm is 0.5 to 0.6. The ratio of the *absorbance* at the maximum at 381 nm to that at the maximum at 405 nm is about 0.9.

B. In the test for Related substances, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH of a 0.9% w/v solution, 7.2 to 8.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Protect the solutions from light and use within 24 hours of preparation, except for solution (4) which should be injected immediately after preparation. Mix 1 volume of a 1% w/v solution of *ammonium acetate*, 1 volume of N-*methylpyrrolidone* and 2 volumes of *methanol* (solution A).

www.webofpharma.com

https://thuocngocanh.com/

(1) Dissolve a quantity of the contents of a sealed container containing the equivalent of 20 mg of amphotericin B in 15 mL of N-*methylpyrrolidone*, immediately dilute to 50 mL with solution A and filter. Dilute 5 volumes of the filtrate to 25 volumes with solution A.

(2) Dissolve 20 mg of *amphotericin B EPCRS* in 15 mL of N-*methylpyrrolidone* and immediately dilute to 50 mL with solution A. Dilute 5 volumes of the resulting solution to 25 volumes with solution A.

(3) Dilute 1 volume of solution (2) to 100 volumes with solution A.

(4) Dissolve 20 mg of *nystatin EPCRS* in 15 mL of N-*methylpyrrolidone* and immediately dilute to 50 mL with solution A. Dilute 5 volumes of the resulting solution to 25 volumes with solution (2) and further dilute 2 volumes to 100 volumes with solution A.

(5) Dissolve 10 mg of *amphotericin B EPCRS* in 5 mL of N-*methylpyrrolidone* and immediately add 35 mL of a mixture of 1 volume of *methanol* and 4 volumes of *absolute ethanol*. Add 0.1 mL of *dilute hydrochloric acid*, mix and incubate at 25° for 2.5 hours. Add 10 mL of a 1% w/v solution of *ammonium acetate* and mix (generation of impurities B and C).

(6) Dissolve 4 mg of *amphotericin B for peak identification EPCRS* (containing impurities A and B) in 5 mL of N-*methylpyrrolidone* and immediately dilute to 50 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (3 µm) (ACE 3 C18 and YMC-Pack Pro are suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use detection wavelengths of 303 nm and 383 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *methanol*, 3 volumes of *acetonitrile* and 6 volumes of a 0.42% w/v solution of *citric acid* previously adjusted to pH 4.7 using *concentrated ammonia*.

Mobile phase B 12 volumes of *methanol*, 20 volumes of a 0.42% w/v solution of *citric acid* previously adjusted to pH 3.9 using *concentrated ammonia* and 68 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-23	100→70	0→30	linear gradient
23-33	70→0	30→100	linear gradient
33-40	0	100	isocratic

Use the chromatogram obtained with solution (6) to identify the peaks due to impurities A and B. When the chromatograms are recorded under the prescribed conditions the retention time of amphotericin B is about 16 minutes. The retention times relative to amphotericin B are: impurity B, about 0.75; impurity A, about 0.8; nystatin, about 0.85.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5) at 383 nm, the *resolution factor* between the peaks due to impurity B and impurity C is at least 1.5.

LIMITS

At a detection wavelength of 303 nm In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (4) (1%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

At a detection wavelength of 383 nm In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (3) (4%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (2%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Total impurities The sum of the impurities detected at 303 nm and 383 nm is not greater than 15%.

Loss on drying

When dried over *phosphorus pentoxide* at 60° at a pressure not exceeding 0.7 kPa, lose not more than 8.0% of their weight. Use 0.3 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of amphotericin B per mL (solution A). The endotoxin limit concentration of solution A is 50 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for Uniformity of weight under Parenteral Preparations of the British Pharmacopoeia, Powders for Injections.

Dissolve a quantity of the mixed contents of the 10 containers containing the equivalent of 50 mg of amphotericin B in 10 mL of *water for injections* and dilute to 100 mL with *dimethyl sulfoxide*. Dilute 5 mL of this solution to 100 mL with a phosphate buffer solution prepared by dissolving 35 g of *dipotassium hydrogen orthophosphate* in sufficient *water* to produce 1000 mL and adjusting the pH, if necessary, to 10.5 with *potassium hydroxide*. Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of amphotericin B in the infusion taking each 1000 IU found to be equivalent to 1 mg of amphotericin B. For a container of average content weight, the upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated content.

STORAGE

Amphotericin for Infusion should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of amphotericin B.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Amphotericin.

© Crown Copyright 2022

www.webofpharma.com

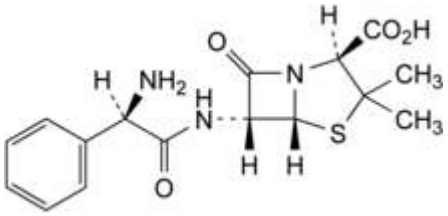
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ampicillin

General Notices

(Ph. Eur. monograph 0167)



$C_{16}H_{19}N_3O_4S$ 349.4 *69-53-4*

Action and use

Penicillin antibacterial.

Preparations

Ampicillin Capsules

Ampicillin Oral Suspension

Ph Eur

DEFINITION

(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-Amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Sparingly soluble in water, practically insoluble in acetone, in ethanol (96 per cent) and in fatty oils. It dissolves in dilute solutions of acids and of alkali hydroxides.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs of *potassium bromide R*.

Comparison *anhydrous ampicillin CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of *sodium hydrogen carbonate solution R*.

Reference solution (a) Dissolve 25 mg of *anhydrous ampicillin CRS* in 10 mL of *sodium hydrogen carbonate solution R*.

Reference solution (b) Dissolve 25 mg of *amoxicillin trihydrate CRS* and 25 mg of *anhydrous ampicillin CRS* in 10 mL of *sodium hydrogen carbonate solution R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 10 volumes of *acetone R* and 90 volumes of a 154 g/L solution of *ammonium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and about 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube in a water-bath for 1 min; a dark yellow colour develops.

www.webofpharma.com

https://thuocngocanh.com/

D. Water (see Tests).

TESTS

Appearance of solution

The solutions are not more opalescent than reference suspension II (*2.2.1*).

Dissolve 1.0 g in 10 mL of *1 M hydrochloric acid*. Separately dissolve 1.0 g in 10 mL of *dilute ammonia R2*. Examine immediately after dissolution.

pH (*2.2.3*)

3.5 to 5.5.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 40 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 280 to + 305 (anhydrous substance).

Dissolve 62.5 mg in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 27.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Test solution (b) *Prepare immediately before use*. Dissolve 27.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 27.0 mg of *anhydrous ampicillin CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dissolve 2.0 mg of *cefradine CRS* in mobile phase A and dilute to 50 mL with mobile phase A. To 5.0 mL of this solution add 5.0 mL of reference solution (a).

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 20.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 0.5 mL of *dilute acetic acid R*, 50 mL of *0.2 M potassium dihydrogen phosphate R* and 50 mL of *acetonitrile R*, then dilute to 1000 mL with *water R*;

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: mix 0.5 mL of *dilute acetic acid R*, 50 mL of *0.2 M potassium dihydrogen phosphate R* and 400 mL of *acetonitrile R*, then dilute to 1000 mL with *water R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	85	15
t_R - (t_R + 30)	85 → 0	15 → 100
(t_R + 30) - (t_R + 45)	0	100
(t_R + 45) - (t_R + 60)	85	15

t_R = retention time of ampicillin determined with reference solution (c)

If the mobile phase composition has been adjusted to achieve the required resolution, the adjusted composition will apply at time zero in the gradient and in the assay.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 50 µL of reference solutions (b) and (c) with isocratic elution at the initial mobile phase composition and 50 µL of test solution (b) according to the elution gradient described under Mobile phase; inject mobile phase A as a blank according to the elution gradient described under Mobile phase.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to ampicillin and cefradin; if necessary, adjust the ratio A:B of the mobile phase.

Limit:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Initial composition of the mixture of mobile phases A and B, adjusted where applicable.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

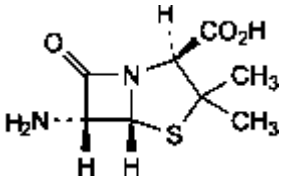
— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{16}H_{19}N_3O_4S$ from the declared content of *anhydrous ampicillin CRS*.

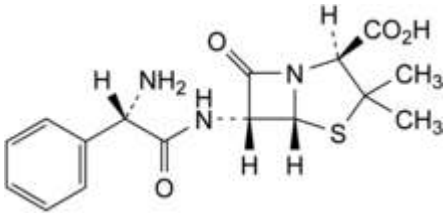
STORAGE

In an airtight container, at a temperature not exceeding 30 °C.

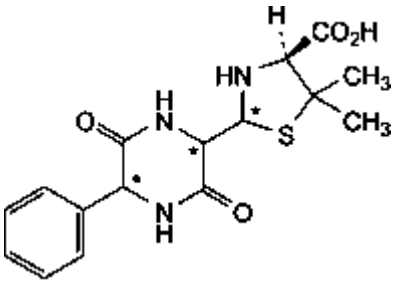
IMPURITIES



A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



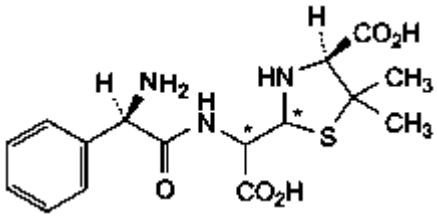
B. (2*S*,5*R*,6*R*)-6-[[(2*S*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-ampicillin),



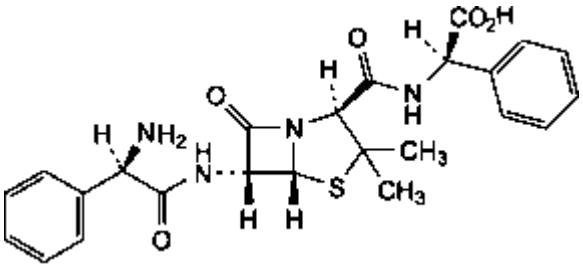
C. (4*S*)-2-(3,6-dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid (diketopiperazines of ampicillin),

www.webofpharma.com

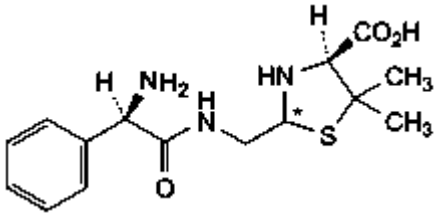
https://thuocngocanh.com/



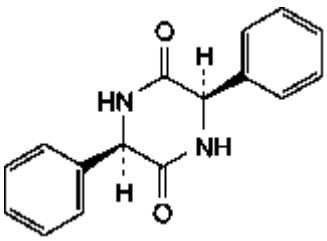
D. (4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]carboxymethyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of ampicillin),



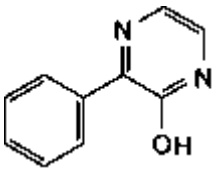
E. (2*R*)-2-[[[(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]-2-phenylacetic acid (ampicillinyl-D-phenylglycine),



F. (2*RS*,4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penilloic acids of ampicillin),



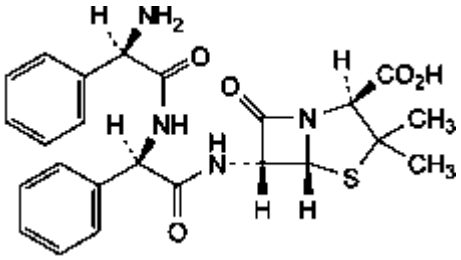
G. (3*R*,6*R*)-3,6-diphenylpiperazine-2,5-dione,



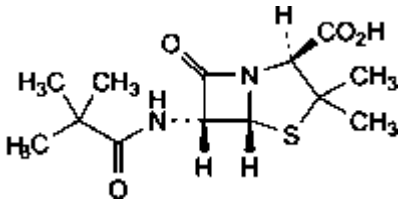
H. 3-phenylpyrazin-2-ol,

www.webofpharma.com

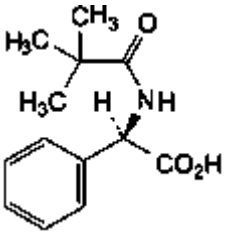
https://thuocngocanh.com/



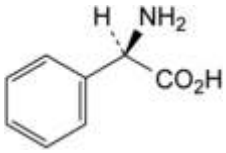
I. (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (D-phenylglycylampicillin),



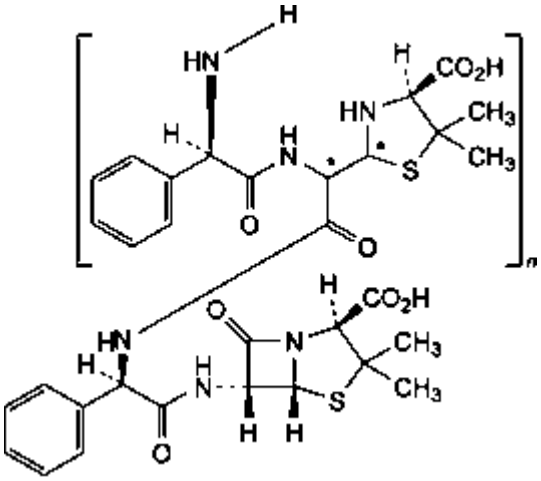
J. (2*S*,5*R*,6*R*)-6-[(2,2-dimethylpropanoyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



K. (2*R*)-2-[(2,2-dimethylpropanoyl)amino]-2-phenylacetic acid,



L. (2*R*)-2-amino-2-phenylacetic acid (D-phenylglycine),



M. co-oligomers of ampicillin and of penicilloic acids of ampicillin.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ampicillin Capsules

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Ampicillin Capsules contain Ampicillin or Ampicillin Trihydrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of ampicillin, $C_{16}H_{19}N_3O_4S$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the capsule contents containing the equivalent of 0.125 g of ampicillin with sufficient *sodium hydrogen carbonate solution* to produce 50 mL and filter.

(2) 0.25% w/v of *ampicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

(3) 0.25% w/v of each of *ampicillin trihydrate BPCRS* and *amoxicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel silanised plate* (Merck silanised silica gel 60 F_{254s} (RP-18) plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose it to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. Suspend a quantity of the capsule contents containing the equivalent of 10 mg of ampicillin in 1 mL of *water* and add 2 mL of a mixture of 2 mL of *cupri-tartaric solution R1* and 6 mL of *water*. A magenta-violet colour is produced immediately.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the mixed capsule contents containing the equivalent of 0.3 g of ampicillin with 80 mL of mobile phase A with the aid of ultrasound for 15 minutes, add sufficient mobile phase A to produce 100 mL and filter through a 0.4-µm filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) 0.025% w/v of *anhydrous ampicillin BPCRS* and 0.002% w/v of *cefradine BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use gradient elution and the mobile phase described below. Equilibrate the column with a mobile phase ratio A:B of 85:15 and use this for the system suitability solution (3). Inject solutions (1) and (2) and start the elution isocratically with the chosen mobile phase. Immediately after elution of the ampicillin peak start the linear gradient elution.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 100 volumes of *acetonitrile* to 2000 volumes with *water*.

Mobile phase B Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 800 volumes of *acetonitrile* to 2000 volumes with *water*.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 → 30	85 → 0	15 → 100	linear gradient
30 → 45	0	100	isocratic
45 → 60	85	15	re-equilibration

Inject mobile phase A and use the same elution gradient to obtain a blank.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to ampicillin and cefradine is at least 3.0. If necessary, adjust the composition of the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the mixed contents of 20 capsules containing the equivalent of 60 mg of ampicillin with 80 mL of solution A for 15 minutes, dilute to 100 mL with the same solvent, filter and dilute 5 mL of the solution to 50 mL with solution A.

(2) 0.006% w/v of *anhydrous ampicillin BPCRS* in solution A.

(3) 0.025% w/v of *anhydrous ampicillin BPCRS* and 0.002% w/v of *cefradine BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

15 volumes of solution B and 85 volumes of solution A.

Solution A Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 100 volumes of *acetonitrile* to 2000 volumes with *water*.

Solution B Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 800 volumes of *acetonitrile* to 2000 volumes with *water*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to ampicillin and cefradine is at least 3.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{19}N_3O_4S$ in the capsules using the declared content of $C_{16}H_{19}N_3O_4S$ in *anhydrous ampicillin BPCRS*.

LABELLING

When the active ingredient is Ampicillin Trihydrate, the quantity is stated in terms of the equivalent amount of ampicillin.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ampicillin Injection

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Ampicillin Injection is a sterile solution of Ampicillin Sodium in Water for Injections. It is prepared by dissolving Ampicillin Sodium for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Ampicillin Injection should be used immediately after preparation.

AMPICILLIN SODIUM FOR INJECTION

DEFINITION

Ampicillin Sodium for Injection is a sterile material consisting of Ampicillin Sodium, with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of ampicillin, $C_{16}H_{19}N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of ampicillin sodium *(RS 366)*. If the spectra are not concordant carry out the following procedure. Dissolve a quantity of the contents of the sealed container containing the equivalent of 0.25 g of ampicillin in 5 mL of *water*, add 0.5 mL of 2M *acetic acid*, mix and allow to stand for 10 minutes in ice. Filter through a sintered-glass filter (ISO 4793, porosity grade 3, is suitable), wash the residue with 2 to 3 mL of a mixture of 9 volumes of *acetone* and 1 volume of *water*, dry at 60° for 30 minutes and prepare a new spectrum of the residue. The spectrum of the residue is concordant with the *reference spectrum* of ampicillin trihydrate *(RS 013)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dissolve a quantity of the contents of the sealed container in sufficient *sodium hydrogen carbonate solution* to produce a solution containing the equivalent of 0.25% w/v of ampicillin.

(2) 0.25% w/v of *ampicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

(3) 0.25% w/v of each of *ampicillin trihydrate BPCRS* and *amoxicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254} silanised plate* (Merck silanised silica gel 60 F_{254s} (RP-18) plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose it to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

A mixture of 10 volumes of *acetone* and 90 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

C. Yield reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Alkalinity

pH of a solution containing the equivalent of 10.0% w/v of ampicillin, 8.0 to 10.0, Appendix V L, measured within 10 minutes of preparing the solution.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the sealed container containing the equivalent of 0.3 g of ampicillin with 80 mL of mobile phase A with the aid of ultrasound for 15 minutes, add sufficient mobile phase A to produce 100 mL and filter through a 0.4-µm filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) Add 1 mL of *water* to 0.2 g of *anhydrous ampicillin BPCRS*. Heat the solution at 60° for 1 hour and dilute 0.5 mL to 50 mL with mobile phase A.

(4) 0.025% w/v of *anhydrous ampicillin BPCRS* and 0.002% w/v of *cefradine BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use gradient elution and the mobile phase described below. Equilibrate the column with a mobile phase ratio A:B of 85:15 and use this mobile phase for the system suitability solution (4). Inject solutions (1), (2) and (3) and start the elution isocratically with the chosen mobile phase. Immediately after elution of the ampicillin peak start the linear gradient elution.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 100 volumes of *acetonitrile* to 2000 volumes with *water*.

Mobile phase B Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 800 volumes of *acetonitrile* to 2000 volumes with *water*.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 → 30	85 → 0	15 → 100	linear gradient
30 → 45	0	100	isocratic
45 → 60	85	15	re-equilibration

Inject mobile phase A and use the same elution gradient to obtain a blank.

SYSTEM SUITABILITY

The chromatogram obtained with solution (3) shows a peak due to ampicillin and a peak due to ampicillin dimer which has a retention time relative to ampicillin of about 2.8.

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to ampicillin and cefradine is at least 3.0. If necessary, adjust the composition of the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to ampicillin dimer is not greater than 4.5 times the area of the principal peak in the chromatogram obtained with solution (2) (4.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Water

www.webofpharma.com

https://thuocngocanh.com/

Not more than 2.0% w/w, Appendix IX C. Use 0.3 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 9.5 mg of ampicillin per mL (solution A). The endotoxin limit concentration of solution A is 1.5 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of the 10 containers in sufficient of solution A to produce a solution containing the equivalent of 0.006% w/v of ampicillin.
(2) 0.006% w/v of *anhydrous ampicillin BPCRS* in solution A.
(3) 0.025% w/v of *anhydrous ampicillin BPCRS* and 0.002% w/v of *cefradine BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

15 volumes of solution B and 85 volumes of solution A.

Solution A Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 100 volumes of *acetonitrile* to 2000 volumes with *water*.

Solution B Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 800 volumes of *acetonitrile* to 2000 volumes with *water*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to ampicillin and cefradine is at least 3.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{19}N_3O_4S$ in a container of average content weight using the declared content of $C_{16}H_{19}N_3O_4S$ in *anhydrous ampicillin BPCRS*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

LABELLING

The label of the sealed container states the quantity of Ampicillin Sodium contained in it in terms of the equivalent amount of ampicillin.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ampicillin Oral Suspension

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Ampicillin Oral Suspension is a suspension of Ampicillin or Ampicillin Trihydrate in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of Water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ampicillin, $C_{16}H_{19}N_3O_4S$

When freshly constituted not more than 120.0% of the stated amount. When stored at the temperature and for the period stated on the label during which the Oral Suspension may be expected to be satisfactory for use, not less than 80.0% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the oral suspension containing the equivalent of 0.125 g of ampicillin with sufficient *sodium hydrogen carbonate solution* to produce 50 mL.

(2) 0.25% w/v of *ampicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

(3) 0.25% w/v of each of *ampicillin trihydrate BPCRS* and *amoxicillin trihydrate BPCRS* in *sodium hydrogen carbonate solution*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel silanised plate* (Merck silanised silica gel 60 F_{254s} (RP-18) plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose it to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 4.0 to 7.0, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral suspension containing the equivalent of 60 mg of ampicillin with sufficient solution A to produce 100 mL and dilute 5 mL of the resulting solution to 50 mL with solution A.
(2) 0.006% w/v of *anhydrous ampicillin BPCRS* in solution A.
(3) 0.025% w/v of *anhydrous ampicillin BPCRS* and 0.002% w/v of *cefradine BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

15 volumes of solution B and 85 volumes of solution A.

Solution A Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 100 volumes of *acetonitrile* to 2000 volumes with *water*.

Solution B Dilute a mixture of 1 volume of *dilute acetic acid*, 100 volumes of 0.2M *potassium dihydrogen orthophosphate* and 800 volumes of *acetonitrile* to 2000 volumes with *water*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to ampicillin and cefradine is at least 3.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{16}H_{19}N_3O_4S$, weight in volume, using the declared content of $C_{16}H_{19}N_3O_4S$ in *anhydrous ampicillin BPCRS*.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The Oral Suspension should be stored at the temperature and used within the period stated on the label.

LABELLING

When the active ingredient is Ampicillin Trihydrate, the quantity is stated in terms of the equivalent amount of ampicillin.

© Crown Copyright 2022

www.webofpharma.com

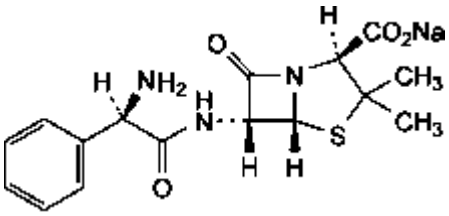
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ampicillin Sodium

General Notices

(Ph. Eur. monograph 0578)



$C_{16}H_{18}N_3NaO_4S$ 371.4 *69-52-3*

Action and use

Penicillin antibacterial.

Preparation

Ampicillin Injection

Ph Eur

DEFINITION

Sodium (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

91.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in acetone, practically insoluble in fatty oils and in liquid paraffin.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 0.250 g in 5 mL of water R, add 0.5 mL of dilute acetic acid R, swirl and allow to stand for 10 min in iced water. Filter the crystals through a small sintered-glass filter (40) (2.1.2), applying suction, wash with 2-3 mL of a mixture of 1 volume of water R and 9 volumes of acetone R, then dry in an oven at 60 °C for 30 min.

Comparison ampicillin trihydrate CRS.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of sodium hydrogen carbonate solution R.

Reference solution (a) Dissolve 25 mg of ampicillin trihydrate CRS in 10 mL of sodium hydrogen carbonate solution R.

Reference solution (b) Dissolve 25 mg of amoxicillin trihydrate CRS and 25 mg of ampicillin trihydrate CRS in 10 mL of sodium hydrogen carbonate solution R.

Plate TLC silanised silica gel plate R.

Mobile phase Mix 10 volumes of acetone R and 90 volumes of a 154 g/L solution of ammonium acetate R previously adjusted to pH 5.0 with glacial acetic acid R.

Application 1 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and about 15 mm in diameter. Moisten with 0.05 mL of water R and add 2 mL of sulfuric acid-formaldehyde reagent R. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube in a water-bath for 1 min; a dark yellow colour develops.

D. It gives reaction (a) of sodium (2.3.1).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solutions A and B are not more opalescent than reference suspension II (2.2.1) and the absorbance (2.2.25) of solution B at 430 nm is not greater than 0.15.

Place 1.0 g in a conical flask and add slowly and with continuous swirling 10 mL of *1 M hydrochloric acid* (solution A). Separately dissolve 1.0 g in *water R* and dilute to 10.0 mL with the same solvent (solution B). Examine immediately after dissolution.

pH (2.2.3)

8.0 to 10.0.

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent. Measure 10 min after dissolution.

Specific optical rotation (2.2.7)

+ 258 to + 287 (anhydrous substance).

Dissolve 62.5 mg in a 4 g/L solution of *potassium hydrogen phthalate R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 31.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Test solution (b) Dissolve 31.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A. *Prepare immediately before use*.

Reference solution (a) Dissolve 27.0 mg of *anhydrous ampicillin CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dissolve 2.0 mg of *cefradine CRS* in mobile phase A and dilute to 50 mL with mobile phase A. To 5.0 mL of this solution add 5.0 mL of reference solution (a).

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 20.0 mL with mobile phase A.

Reference solution (d) To 0.20 g of the substance to be examined add 1.0 mL of *water R*. Heat the solution at 60 °C for 1 h. Dilute 0.5 mL of this solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 0.5 mL of *dilute acetic acid R*, 50 mL of *0.2 M potassium dihydrogen phosphate R* and 50 mL of *acetonitrile R*, then dilute to 1000 mL with *water R*;

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *mobile phase B*: mix 0.5 mL of *dilute acetic acid R*, 50 mL of *0.2 M potassium dihydrogen phosphate R* and 400 mL of *acetonitrile R*, then dilute to 1000 mL with *water R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	85	15
t_R - (t_R + 30)	85 → 0	15 → 100
(t_R + 30) - (t_R + 45)	0	100
(t_R + 45) - (t_R + 60)	85	15

t_R = retention time of ampicillin determined with reference solution (c)

If the mobile phase composition has been adjusted to achieve the required resolution, the adjusted composition will apply at time zero in the gradient and in the assay.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 50 µL of reference solutions (b) and (c) with isocratic elution at the initial mobile phase composition and 50 µL of test solution (b) and reference solution (d) according to the elution gradient described under Mobile phase; inject mobile phase A as a blank according to the elution gradient described under Mobile phase.

Identification of peaks Use the chromatogram obtained with reference solution (d) to identify the peaks due to ampicillin and ampicillin dimer.

Relative retention With reference to ampicillin: ampicillin dimer = about 2.8.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to ampicillin and cefradin; if necessary adjust the ratio A:B of the mobile phase.

Limits:

— *ampicillin dimer*: not more than 4.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (4.5 per cent);

— *any other impurity*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (2 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

www.webofpharma.com

https://thuocngocanh.com/

2-Ethylhexanoic acid (2.4.28)

Maximum 0.8 per cent *m/m*.

Methylene chloride

Gas chromatography (2.2.28).

Internal standard solution Dissolve 1.0 mL of *ethylene chloride R* in *water R* and dilute to 500.0 mL with the same solvent.

Test solution (a) Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Test solution (b) Dissolve 1.0 g of the substance to be examined in *water R*, add 1.0 mL of the internal standard solution and dilute to 10.0 mL with *water R*.

Reference solution Dissolve 1.0 mL of *methylene chloride R* in *water R* and dilute to 500.0 mL with the same solvent. To 1.0 mL of this solution add 1.0 mL of the internal standard solution and dilute to 10.0 mL with *water R*.

Column:

— *material*: glass;

— *size*: *l* = 1.5 m, Ø = 4 mm;

— *stationary phase*: *diatomaceous earth for gas chromatography R* impregnated with 10 per cent *m/m* of *macrogol 1000 R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 40 mL/min.

Temperature:

— *column*: 60 °C;

— *injection port*: 100 °C;

— *detector*: 150 °C.

Detection Flame ionisation.

Calculate the content of methylene chloride taking its density at 20 °C to be 1.325 g/mL.

Limit:

— *methylene chloride*: maximum 0.2 per cent *m/m*.

Water (2.5.12)

Maximum 2.0 per cent, determined on 0.300 g.

www.webofpharma.com

https://thuocngocanh.com/

Bacterial endotoxins (*2.6.14*)

Less than 0.15 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Initial composition of the mixture of mobile phases A and B, adjusted where applicable.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

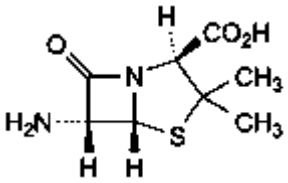
— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of ampicillin sodium by multiplying the percentage content of ampicillin by 1.063.

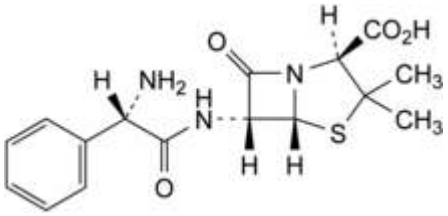
STORAGE

In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES



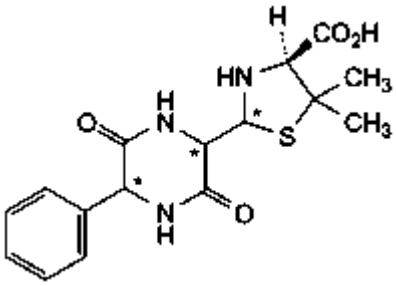
A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



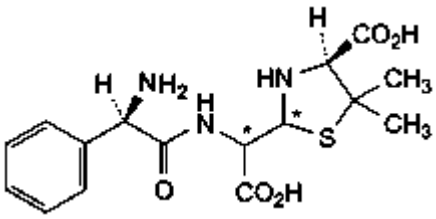
B. (2*S*,5*R*,6*R*)-6-[[(2*S*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-ampicillin),

www.webofpharma.com

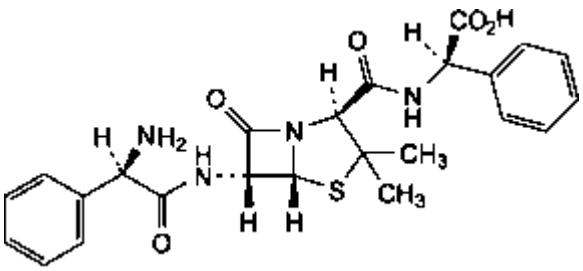
https://thuocngocanh.com/



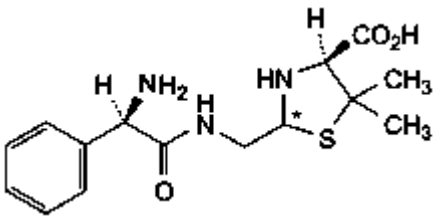
C. (4*S*)-2-(3,6-dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid (diketopiperazines of ampicillin),



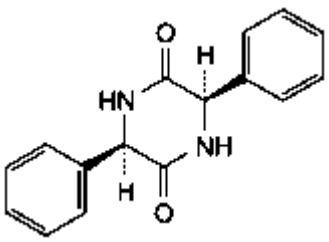
D. (4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of ampicillin),



E. (2*R*)-2-[[[(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]-2-phenylacetic acid (ampicillinyl-D-phenylglycine),



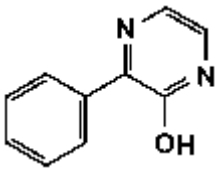
F. (2*RS*,4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of ampicillin),



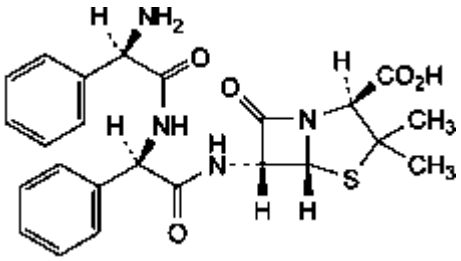
G. (3*R*,6*R*)-3,6-diphenylpiperazine-2,5-dione,

www.webofpharma.com

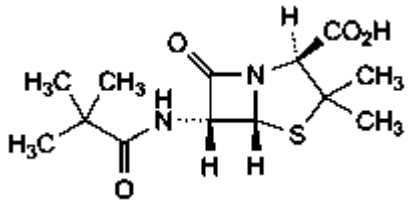
https://thuocngocanh.com/



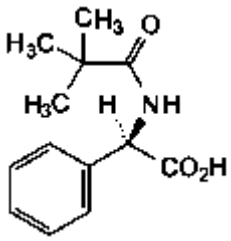
H. 3-phenylpyrazin-2-ol,



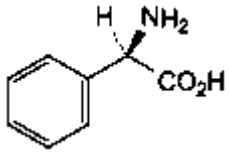
I. (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia1-azabicyclo[3.2.0]heptane-2-carboxylic acid (D-phenylglycylampicillin),



J. (2*S*,5*R*,6*R*)-6-[(2,2-dimethylpropanoyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



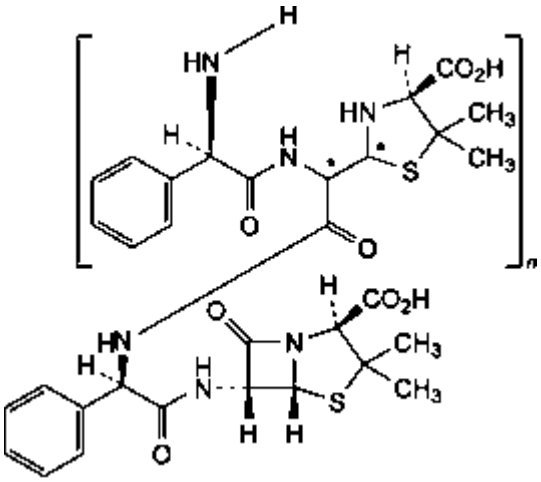
K. (2*R*)-2-[(2,2-dimethylpropanoyl)amino]-2-phenylacetic acid,



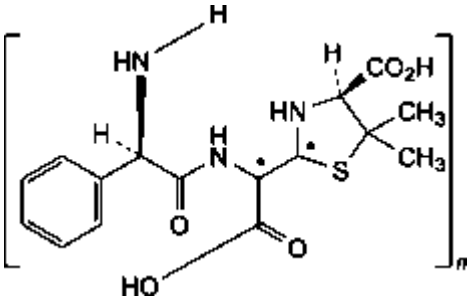
L. (2*R*)-2-amino-2-phenylacetic acid (D-phenylglycine),

www.webofpharma.com

https://thuocngocanh.com/



M. co-oligomers of ampicillin and of penicilloic acids of ampicillin,



N. oligomers of penicilloic acids of ampicillin.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

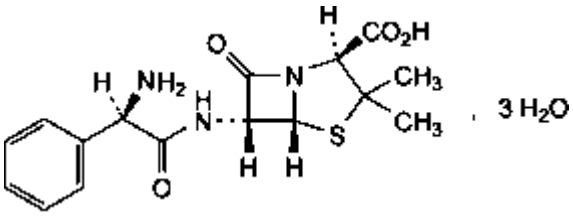
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ampicillin Trihydrate

General Notices

(Ph. Eur. monograph 0168)



$C_{16}H_{19}N_3O_4S,3H_2O$ 403.5 *7177-48-2*

Action and use

Penicillin antibacterial.

Preparations

Ampicillin Capsules

Ampicillin Oral Suspension

Co-fluampicil Capsules

Co-fluampicil Oral Suspension

Ph Eur

DEFINITION

(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-Amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent) and in fatty oils. It dissolves in dilute solutions of acids and of alkali hydroxides.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ampicillin trihydrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of *sodium hydrogen carbonate solution R*.

Reference solution (a) Dissolve 25 mg of *ampicillin trihydrate CRS* in 10 mL of *sodium hydrogen carbonate solution R*.

Reference solution (b) Dissolve 25 mg of *amoxicillin trihydrate CRS* and 25 mg of *ampicillin trihydrate CRS* in 10 mL of *sodium hydrogen carbonate solution R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 10 volumes of *acetone R* and 90 volumes of a 154 g/L solution of *ammonium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and about 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube in a water-bath for 1 min; a dark yellow colour develops.

D. Water (see Tests).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Appearance of solution

The solutions are not more opalescent than reference suspension II (*2.2.1*).

Dissolve 1.0 g in 10 mL of *1 M hydrochloric acid*. Separately dissolve 1.0 g in 10 mL of *dilute ammonia R2*. Examine immediately after dissolution.

pH (*2.2.3*)

3.5 to 5.5.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 40 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 280 to + 305 (anhydrous substance).

Dissolve 62.5 mg in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 31.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Test solution (b) Dissolve 31.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A. *Prepare immediately before use.*

Reference solution (a) Dissolve 27.0 mg of *anhydrous ampicillin CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dissolve 2 mg of *cefradine CRS* in mobile phase A and dilute to 50 mL with mobile phase A. To 5 mL of this solution, add 5 mL of reference solution (a).

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 20.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 0.5 mL of *dilute acetic acid R*, 50 mL of *0.2 M potassium dihydrogen phosphate R* and 50 mL of *acetonitrile R*, then dilute to 1000 mL with *water R*;

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: mix 0.5 mL of *dilute acetic acid R*, 50 mL of *0.2 M potassium dihydrogen phosphate R* and 400 mL of *acetonitrile R*, then dilute to 1000 mL with *water R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	85	15
t_R - (t_R + 30)	85 → 0	15 → 100
(t_R + 30) - (t_R + 45)	0	100
(t_R + 45) - (t_R + 60)	85	15

t_R = retention time of ampicillin determined with reference solution (c)

If the mobile phase composition has been adjusted to achieve the required resolution, the adjusted composition will apply at time zero in the gradient and in the assay.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 50 µL of reference solutions (b) and (c) with isocratic elution at the initial mobile phase composition and 50 µL of test solution (b) according to the elution gradient described under Mobile phase; inject mobile phase A as a blank according to the elution gradient described under Mobile phase.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to ampicillin and cefradin; if necessary, adjust the ratio A:B of the mobile phase.

Limit:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

Water (*2.5.12*)

12.0 per cent to 15.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Initial composition of the mixture of mobile phases A and B, adjusted where applicable.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

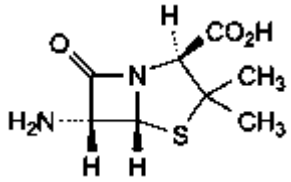
— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of ampicillin from the declared content of *anhydrous ampicillin CRS*.

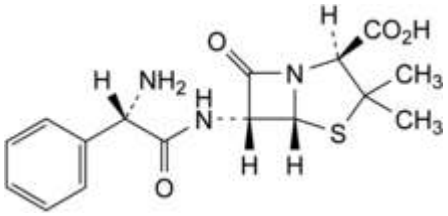
STORAGE

In an airtight container.

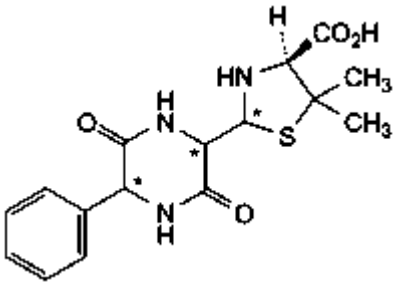
IMPURITIES



A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



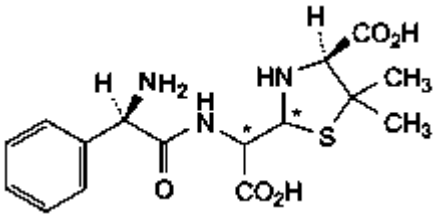
B. (2*S*,5*R*,6*R*)-6-[[(2*S*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-ampicillin),



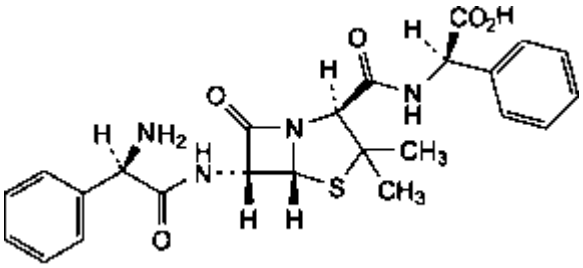
C. (4*S*)-2-(3,6-dioxo-5-phenylpiperazin-2-yl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (diketopiperazines of ampicillin),

www.webofpharma.com

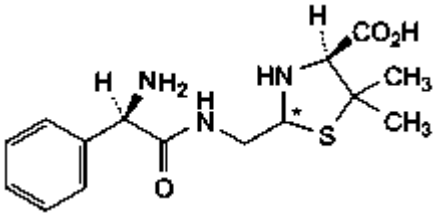
https://thuocngocanh.com/



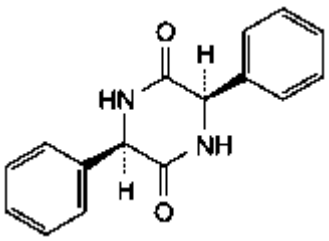
D. (4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]carboxymethyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of ampicillin),



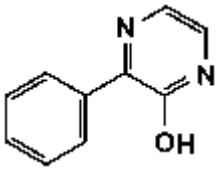
E. (2*R*)-2-[[[(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]-2-phenylacetic acid (ampicillinyl-D-phenylglycine),



F. (2*RS*,4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penilloic acids of ampicillin),



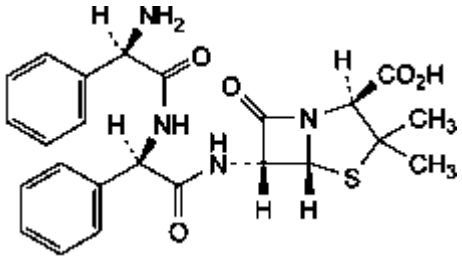
G. (3*R*,6*R*)-3,6-diphenylpiperazine-2,5-dione,



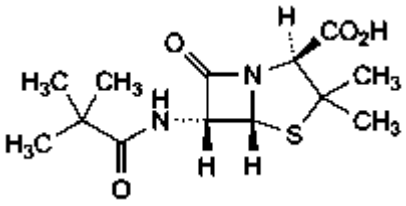
H. 3-phenylpyrazin-2-ol,

www.webofpharma.com

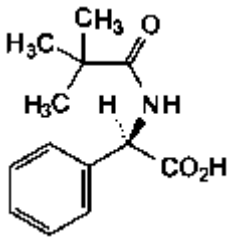
https://thuocngocanh.com/



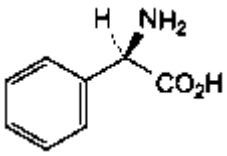
I. (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (D-phenylglycylampicillin),



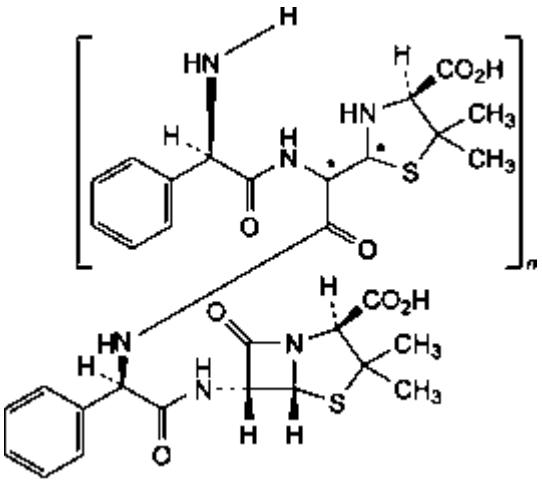
J. (2*S*,5*R*,6*R*)-6-[(2,2-dimethylpropanoyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



K. (2*R*)-2-[(2,2-dimethylpropanoyl)amino]-2-phenylacetic acid,



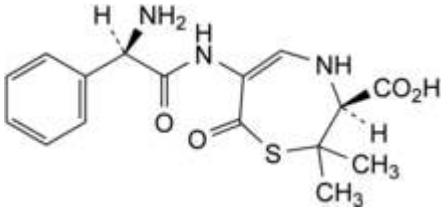
L. (2*R*)-2-amino-2-phenylacetic acid (D-phenylglycine),



www.webofpharma.com

https://thuvienthuocngocanh.com/

M. co-oligomers of ampicillin and of penicilloic acids of ampicillin,



N. (3*S*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2,2-dimethyl-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine-3-carboxylic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

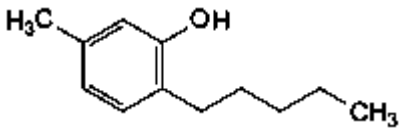
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Amylmetacresol

General Notices

(Ph. Eur. monograph 2405)



$C_{12}H_{18}O$ 178.3 *1300-94-3*

Action and use

Antiseptic.

Ph Eur

DEFINITION

5-Methyl-2-pentylphenol.

Content

98.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

Clear or almost clear liquid, or solid crystalline mass, colourless or slightly yellow when freshly prepared. The substance changes colour during storage by darkening and/or discolouration to dark yellow, brownish-yellow or pink.

Solubility

Practically insoluble in water, very soluble in acetone and in ethanol (96 per cent).

It solidifies at about 22 °C.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *amylmetacresol CRS*.

TESTS

Related substances

Gas chromatography (2.2.28): use the normalisation procedure.

Internal standard solution Dissolve 0.100 g of *butylhydroxytoluene R* in *2-propanol R* and dilute to 10.0 mL with the same solvent.

Test solution (a) Dissolve 0.100 g of the substance to be examined in *2-propanol R* and dilute to 10.0 mL with the same solvent.

Test solution (b) To 2.0 mL of test solution (a) add 2.0 mL of the internal standard solution and dilute to 10.0 mL with *2-propanol R*.

Reference solution (a) Dissolve 10 mg of *m-cresol R* (impurity B) and 10 mg of *p-cresol R* (impurity D) in *2-propanol R* and dilute to 100 mL with the same solvent.

Reference solution (b) Dissolve the contents of a vial of *amylmetacresol for peak identification A CRS* (containing impurities A and G) in 1 mL of *2-propanol R*.

Reference solution (c) Dissolve 0.100 g of *amylmetacresol CRS* in *2-propanol R* and dilute to 10.0 mL with the same solvent. To 2.0 mL of this solution add 2.0 mL of the internal standard solution and dilute to 10.0 mL with *2-propanol R*.

Reference solution (d) Dilute 1.0 mL of test solution (a) to 100.0 mL with *2-propanol R*. Dilute 1.0 mL of this solution to 20.0 mL with *2-propanol R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 33 cm/s.

Split ratio 1:30.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 17.5	100 → 240

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
	17.5 - 32.5	240
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1.0 µL of test solution (a) and reference solutions (a), (b) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and D; use the chromatogram supplied with *amylmetacresol for peak identification A CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and G.

Relative retention With reference to amylmetacresol (retention time = about 16 min): impurity G (diastereoisomer 1) = about 0.51; impurity G (diastereoisomer 2) = about 0.53; impurity D = about 0.77; impurity B = about 0.78; impurity A = about 0.99.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities D and B.

Limits:

— *impurity A*: maximum 0.6 per cent;

— *impurity G*: maximum 0.15 per cent for the sum of the 2 diastereoisomers;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *disregard limit*: the area of the peak due to amylmetacresol in the chromatogram obtained with reference solution (d) (0.05 per cent).

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (*2.2.28*) as described in the test for related substances with the following modification.

Injection 1.0 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_{12}H_{18}O$ taking into account the assigned content of *amylmetacresol CRS*.

STORAGE

www.webofpharma.com

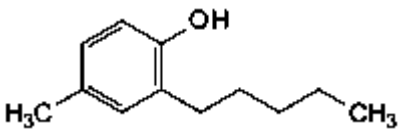
https://thuocngocanh.com/

In an airtight, non-metallic container, protected from light.

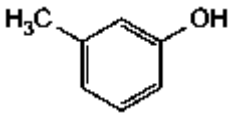
IMPURITIES

Specified impurities A, G.

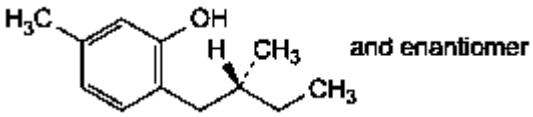
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, F, H, I, J.



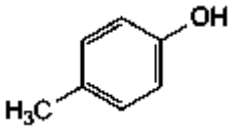
A. 4-methyl-2-pentylphenol,



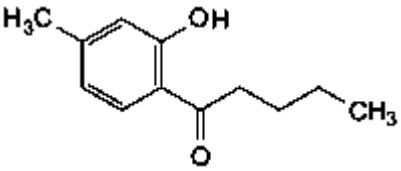
B. 3-methylphenol (*m*-cresol),



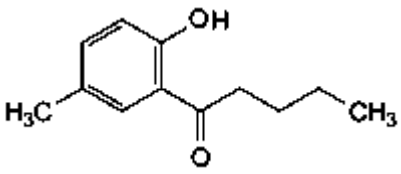
C. 5-methyl-2-[(2*RS*)-2-methylbutyl]phenol,



D. 4-methylphenol (*p*-cresol),



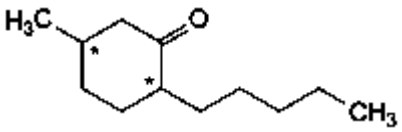
E. 1-(2-hydroxy-4-methylphenyl)pentan-1-one,



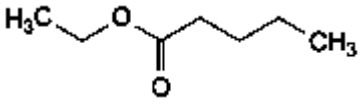
www.webofpharma.com

https://thuocngocanh.com/

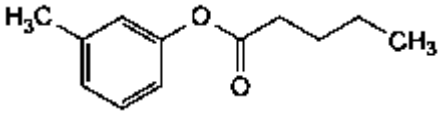
F. 1-(2-hydroxy-5-methylphenyl)pentan-1-one,



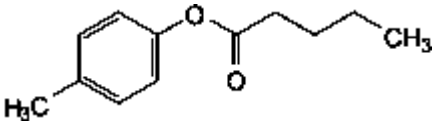
G. (2Ξ,5Ξ)-5-methyl-2-pentylcyclohexan-1-one,



H. ethyl pentanoate,



I. 3-methylphenyl pentanoate,



J. 4-methylphenyl pentanoate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Anaesthetic Ether

General Notices

(Ph. Eur. monograph 0367)

Removed in version 11.2

© Crown Copyright 2022

www.webofpharma.com

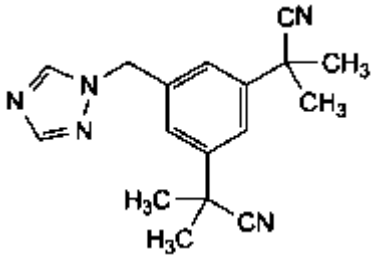
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Anastrozole

General Notices

(Ph. Eur. monograph 2406)



$C_{17}H_{19}N_5$ 293.4 *120511-73-1*

Action and use

Aromotase inhibitor; treatment of breast carcinoma.

Preparation

Anastrozole Tablets

Ph Eur

DEFINITION

2,2′-[5-(1*H*-1,2,4-Triazol-1-ylmethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile).

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, freely soluble in anhydrous ethanol, practically insoluble in cyclohexane.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison anastrozole CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, water for chromatography R (50:50 *V/V*).

Test solution (a) Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.5 mg of anastrozole impurity E CRS in 20.0 mL of the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with test solution (a).

Reference solution (c) Dissolve 25.0 mg of anastrozole CRS in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped ethylene-bridged polar-embedded octadecylsilyl silica gel for chromatography (hybrid material) R (3.5 µm).

Mobile phase:

— *mobile phase A*: phosphoric acid R, water for chromatography R (0.1:100 *V/V*);

— *mobile phase B*: phosphoric acid R, acetonitrile R1 (0.1:100 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	95	5
2 - 54	95 → 35	5 → 65

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention With reference to anastrozole (retention time = about 29 min): impurity E = about 1.05.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to anastrozole and impurity E.

Calculation of percentage contents:

— for each impurity, use the concentration of anastrozole in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

Maximum 0.3 per cent, determined on 50.0 mg.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

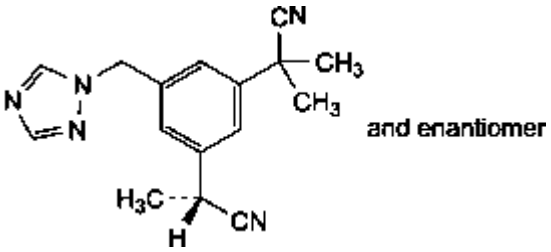
Calculate the percentage content of $C_{17}H_{19}N_5$ taking into account the assigned content of *anastrozole CRS*.

IMPURITIES

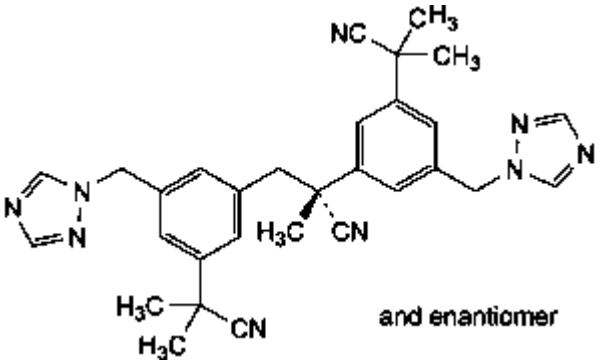
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H, I.*

www.webofpharma.com

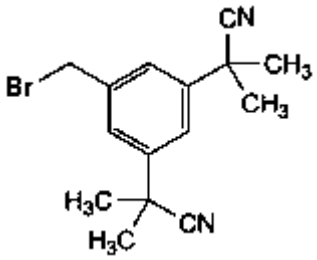
https://thuocngocanh.com/



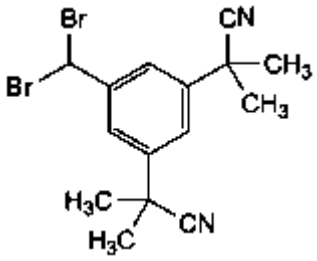
A. 2-[3-[(1*RS*)-1-cyanoethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile,



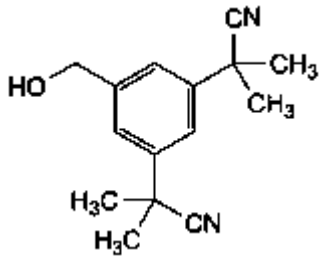
B. (2*RS*)-2,3-bis[3-(1-cyano-1-methylethyl)-5-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile,



C. 2,2′-[5-(bromomethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile),



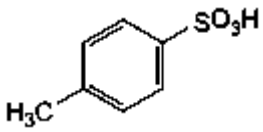
D. 2,2′-[5-(dibromomethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile),



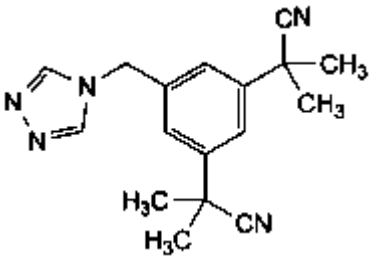
www.webofpharma.com

https://thuocngocanh.com/

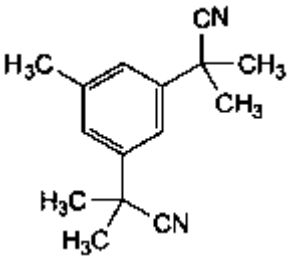
E. 2,2′-[5-(hydroxymethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile),



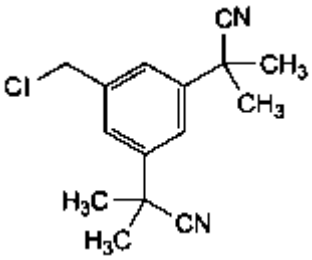
F. 4-methylbenzenesulfonic acid,



G. 2,2′-[5-(4*H*-1,2,4-triazol-4-ylmethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile),



H. 2,2′-(5-methylbenzene-1,3-diyl)bis(2-methylpropanenitrile),



I. 2,2′-[5-(chloromethyl)benzene-1,3-diyl]bis(2-methylpropanenitrile).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Anastrozole Tablets

General Notices

Action and use

Aromatase inhibitor; treatment of breast carcinoma.

DEFINITION

Anastrozole Tablets contain Anastrozole.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anastrozole, $C_{17}H_{19}N_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 8 mg of Anastrozole add 10 mL of *diethyl ether*, mix with the aid of ultrasound and filter through a 0.45-µm filter (Nylon 66 is suitable). Add 0.4 g of *potassium bromide* to the residue and evaporate to dryness under a stream of nitrogen. Dry under vacuum at 50° for 1 hour. Triturate the residue with a further 0.4 g of *potassium bromide*. The *infrared absorption spectrum* of the powder, Appendix II A, is concordant with the *reference spectrum* of anastrozole *(RS 493)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, to produce a solution expected to contain 0.0001% w/v of Anastrozole.
(2) Dilute a 0.25% w/v solution of *anastrozole BPCRS* in *acetonitrile R1* with sufficient *water* to produce a solution containing 0.0001% w/v of anastrozole.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.25% w/v *anastrozole BPCRS* and 0.075% w/v *methyl parahydroxybenzoate* in *acetonitrile R1*. Dilute with *water* to produce a solution containing 0.0001% w/v of anastrozole and 0.00003% w/v of methyl parahydroxybenzoate.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 3.2 mm) packed with octylsilyl and octadecylsilyl multi-alkyl silica gel for chromatography (5 µm) (Hichrom RPB C8/C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.75 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 100 µL of each solution.

MOBILE PHASE

1 volume of *trifluoroacetic acid*, 300 volumes of *acetonitrile R1* and 700 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between methyl parahydroxybenzoate and anastrozole is at least 4.0.

DETERMINATION OF CONTENT

Calculate the total content of anastrozole, $C_{17}H_{19}N_5$, in the medium from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_5$ in *anastrozole BPCRS*.

LIMITS

The amount of anastrozole released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of whole tablets containing 25 mg of Anastrozole with 80 mL of 50% v/v *acetonitrile R1*, mix with the aid of ultrasound, dilute to 100 mL with 50% v/v *acetonitrile R1* and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with 50% v/v *acetonitrile R1*.
(3) Dissolve the contents of a vial of *anastrozole impurity E EPCRS* to 100 mL of 50% v/v *acetonitrile R1*. Dilute 1 volume of the resulting solution to 50 volumes with solution (2).
(4) Dilute 1 volume of solution (2) to 5 volumes with 50% v/v *acetonitrile R1*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (XBridge Shield RP 18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1 volume of *orthophosphoric acid* and 100 volumes of *water*.

Mobile phase B 0.1 volume of *orthophosphoric acid* and 100 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	95	5	isocratic
2-54	95→35	5→65	linear gradient
54-55	35→95	65→5	linear gradient
55-65	95	5	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to anastrozole (retention time about 30 minutes) are: impurity F, about 0.38; impurity G, about 0.86; impurity A, about 0.93; impurity E, about 1.04; impurity B, about 1.11; impurity H, about 1.48; impurity I, about 1.50; impurity C, about 1.55; impurity D, about 1.65.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to anastrozole and impurity E is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of Content

Tablets containing less than 2 mg and/or less than 2% w/w of Anastrozole must comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.1 volumes of *trifluoroacetic acid*, 100 volumes of *acetonitrile R1* and 100 volumes of *water*.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake 1 tablet with a sufficient volume of solution A to produce a solution expected to contain 0.01% w/v of Anastrozole and filter.

(2) 0.01% w/v of *anastrozole BPCRS* in solution A.

(3) 0.01% w/v of *anastrozole BPCRS* and 0.06% w/v of *methyl parahydroxybenzoate* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with an injection volume of 10 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methyl parahydroxybenzoate and anastrozole is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_5$ in each tablet from the chromatograms obtained using the declared content of $C_{17}H_{19}N_5$ in *anastrozole BPCRS*

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of anastrozole

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of anastrozole

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B 0.8 volumes of *trifluoroacetic acid*, 200 volumes of *acetonitrile R1* and 800 volumes of *water*.

(1) Shake 10 tablets with 60 mL of mobile phase. Dilute, if necessary, with mobile phase to produce a solution containing 0.01% w/v Anastrozole and filter.

(2) 0.01% w/v of *anastrozole BPCRS* in solution B.

(3) 0.01% w/v of *anastrozole BPCRS* and 0.006% w/v *methyl parahydroxybenzoate* in solution B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with an injection volume of 10 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methyl parahydroxybenzoate and anastrozole is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_5$ in the tablets using the declared content of $C_{17}H_{19}N_5$ in *anastrozole BPCRS*

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Anastrozole.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

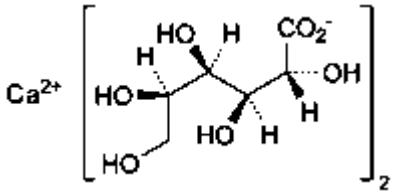
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Anhydrous Calcium Gluconate

General Notices

(Ph. Eur. monograph 2364)



$C_{12}H_{22}CaO_{14}$ 430.4

Action and use

Used in treatment of calcium deficiency.

Ph Eur

DEFINITION

Calcium bis[(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate] (calcium di(D-gluconate)).

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or granular powder.

Solubility

Sparingly soluble in water, freely soluble in boiling water.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of *water R*, heating if necessary in a water-bath at 60 °C.

Reference solution Dissolve 20 mg of *calcium gluconate CRS* in 1 mL of *water R*, heating if necessary in a water-bath at 60 °C.

www.webofpharma.com

https://thuocngocanh.com/

Plate TLC silica gel plate R (5-40 µm) [or TLC silica gel plate R (2-10 µm)].

Mobile phase concentrated ammonia R, ethyl acetate R, water R, ethanol (96 per cent) R (10:10:30:50 *V/V/V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying At 100 °C for 20 min, then allow to cool.

Detection Spray with a solution containing 25 g/L of ammonium molybdate R and 10 g/L of cerium sulfate R in dilute sulfuric acid R, and heat at 100-105 °C for about 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Solution S (see Tests) gives reaction (b) of calcium (2.3.1).

C. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 1.0 g in water R heated to 60 °C and dilute to 50 mL with the same solvent.

Appearance of solution

At 60 °C, solution S is not more intensely coloured than reference solution Y_6 (2.2.2, Method II). After cooling, it is not more opalescent than reference suspension II (2.2.1).

Organic impurities and boric acid

Place 0.5 g in a porcelain dish previously rinsed with sulfuric acid R and placed in a bath of iced water. Add 2 mL of cooled sulfuric acid R and mix. No yellow or brown colour develops. Add 1 mL of chromotrope II B solution R. A violet colour develops and does not become dark blue. Compare the colour obtained with that of a mixture of 1 mL of chromotrope II B solution R and 2 mL of cooled sulfuric acid R.

Sucrose and reducing sugars

Dissolve 0.5 g in a mixture of 2 mL of hydrochloric acid R1 and 10 mL of water R. Boil for 5 min, allow to cool, add 10 mL of sodium carbonate solution R and allow to stand for 10 min. Dilute to 25 mL with water R and filter. To 5 mL of the filtrate add 2 mL of cupri-tartaric solution R and boil for 1 min. Allow to stand for 2 min. No red precipitate is formed.

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 12.5 mL of solution S to 15 mL with water R.

www.webofpharma.com

https://thuocngocanh.com/

Sulfates (*2.4.13*)

Maximum 100 ppm.

Dissolve 10.0 g with heating in a mixture of 10 mL of *acetic acid R* and 90 mL of *distilled water R*.

Magnesium and alkali metals

Maximum 0.4 per cent (expressed as MgO).

Dissolve 1.00 g in 100 mL of boiling *water R*, add 10 mL of *ammonium chloride solution R*, 1 mL of *ammonia R* and, dropwise, 50 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 200 mL with *water R* and filter. Evaporate 100 mL of the filtrate to dryness and ignite. The residue weighs a maximum of 2 mg.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 16 h.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

ASSAY

Dissolve 0.350 g in 20 mL of hot *water R*, allow to cool and dilute to 300 mL with *water R*. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 43.04 mg of $C_{12}H_{22}CaO_{14}$.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Anhydrous Sodium Sulfate

General Notices

Anhydrous Sodium Sulphate

(Ph. Eur. monograph 0099)

Na_2SO_4 142.0 *7757-82-6*

Action and use

Laxative.

Ph Eur

DEFINITION

Anhydrous disodium sulfate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Freely soluble in water.

IDENTIFICATION

A. It gives reaction (a) of sulfates (*2.3.1*).

B. It gives reaction (a) of sodium (*2.3.1*).

C. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 2.2 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (*2.4.4*)

Maximum 450 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Calcium (*2.4.3*)

Maximum 450 ppm, if intended for use in the manufacture of parenteral preparations.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 90 ppm, if intended for use in the manufacture of parenteral preparations.

Dilute 5 mL of solution S to 10 mL with *water R*.

Magnesium

Maximum 200 ppm, if intended for use in the manufacture of parenteral preparations.

To 10 mL of solution S add 1 mL of *glycerol (85 per cent) R*, 0.15 mL of *titan yellow solution R*, 0.25 mL of *ammonium oxalate solution R* and 5 mL of *dilute sodium hydroxide solution R* and shake. Any pink colour in the test solution is not more intense than that in a standard prepared at the same time in the same manner using a mixture of 5 mL of *magnesium standard solution (10 ppm Mg) R* and 5 mL of *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 130 °C.

ASSAY

Pack 20 g of *strongly acidic ion-exchange resin R* into a glass column, at least 20 cm long and 20 mm in internal diameter, and cover it with *water R*. After 5 min, wash the resin with *water R* until the pH of the eluate is about 6 to 7 using a *pH indicator strip R*. Keep the resin covered with *water R*. Dissolve 0.500 g of the substance to be examined in 10 mL of *water R* in a beaker. Load the solution onto the column and pass through the resin at a flow rate of about 4 mL/min until the resin is just covered with the solution. Using about 200 mL of *water R*, rinse the beaker and pass the rinsings through the column at the same flow rate. Check that the pH of the last eluate is about 6 to 7 using a *pH indicator strip R*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Titrate the eluate with *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *1 M sodium hydroxide* is equivalent to 71.00 mg of Na_2SO_4.

STORAGE

Store in an airtight container.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Animal Epithelia and Outgrowths for Allergen Products

General Notices

(Ph. Eur. monograph 2621)

Ph Eur

DEFINITION

Animal epithelia and outgrowths for allergen products consist of hair, epithelium fragments, dander, feathers and other structures that grow from the epidermis of mammals or birds.

Animal epithelia and outgrowths may contain proteins deposited from the saliva and/or secretions from the sebaceous glands of the animal. They may be further processed (e.g. cut or washed) using qualified methods or are unprocessed.

PRODUCTION

Animal epithelia and outgrowths for allergen products are obtained from healthy animals selected to avoid possible transmissible agents of disease. The exact species and/or variety of animal is stated. Typical production steps, including animal management, source material collection and purification, are specified. The origin, quality, and traceability of the source material must be demonstrated.

It is expected that, where applicable, the animal care and husbandry follows the principles described for the protection of vertebrate animals used for experimental and other scientific purposes. A responsible veterinarian or another competent person confirms the identity of the species and that the animals are healthy. It is verified that the skin is visibly clean and intact before harvest and that the animals have not been recently treated with preparations for cutaneous application, such as antiparasitic drugs.

The collection of animal epithelia and outgrowths must be performed without injuring the skin of the animal. Confirmation that measures are in place to prevent cross-contamination by animal epithelia and outgrowths from other animals is provided, including during animal management, collection and processing. Methods involving the grinding of whole skin and/or pelts must not be used.

Where major changes to the production of the animal epithelia and outgrowths take place (e.g. when a new process or supplier is introduced), such changes are qualified.

Microbial contamination of the animal epithelia and outgrowths may be unavoidable and should be monitored on a representative number of batches of source material according to a justified sampling plan and each time a new supplier and/or a new process for the source material production is introduced; if a determination of microbial contamination is not applicable, this must be justified. Microbial contamination values and potential increases in microbial contamination are monitored during stability studies, in order to assess this aspect along with the source material characteristics upon storage.

Control methods and acceptance criteria relating to identity and purity of the animal epithelia and outgrowths are established. The acceptance criteria must ensure the consistency of the animal epithelia and outgrowths source material from a qualitative and quantitative

www.webofpharma.com

https://thuvienthuocngocanh.com/

point of view. The animal epithelia and outgrowths source material is stored under controlled conditions justified by stability data. The collection and production, as well as the handling of the source material, are such that consistent composition is ensured from batch to batch.

ANIMAL EPITHELIA AND OUTGROWTHS FOR ALLERGEN PRODUCTS REFERENCE BATCH

An appropriate reference batch is established for each animal epithelia and outgrowths source material. The nature of the reference batch depends on the testing approach to verify batch-to-batch consistency and to establish acceptable quality. The reference batch may be, for example, an internal reference preparation (if available), a source material extract or a sample of a production batch. Its characterisation must be described. The extent of characterisation of the reference batch depends on the nature of the animal epithelia and outgrowths source material, knowledge of the allergenic components and availability of suitable reagents. The reference batch is stored under controlled conditions ensuring its stability.

BATCH-TO-BATCH CONSISTENCY

To establish batch-to-batch consistency, one or more of the following tests are performed on each batch. The choice of tests must be justified.

Total protein (*2.5.33*)

Protein profile

Determined by using suitable electrophoresis methods (*2.2.31*, *2.2.54*).

Allergen profile

Relevant allergenic components are identified by means of suitable techniques using allergen-specific antibodies.

Major allergen content

Determined by using suitable immunochemical methods (*2.7.1*) such as enzyme-linked immunosorbent assay (ELISA).

Total allergenic activity

Determined by testing inhibition of the binding capacity of specific immunoglobulin E antibodies or by a suitable equivalent *in vitro* method.

CHARACTERS

Animal epithelia and outgrowths for allergen products are supplied as coloured powders or other materials such as feathers, dander or hairs.

IDENTIFICATION

The identity of animal epithelia and outgrowths is confirmed by their relevant macroscopic and microscopic characteristics in comparison to those of a reference batch or reference documents. Identity may also be confirmed using other methods such as ELISA or by genetic identification, if performed by generally accepted methods.

www.webofpharma.com

https://thuvienthuocngocanh.com/

TESTS

Foreign matter

Foreign matter is defined as vermin (e.g. mites and fleas), dirt, and foreign animal epithelia and outgrowths. Foreign matter is determined by appropriate tests (e.g. microscopic examination, ELISA), visual inspection and/or tactile inspection. Foreign matter is below a predefined and justified limit.

Water (*2.5.12* or *2.5.32*) or loss on drying (*2.2.32*)

The water content of dried material is determined; specification limits must be supported by batch analysis and stability data.

STORAGE

The source materials are stored under controlled conditions justified by stability data.

LABELLING

The label states:

— the species of the source animal;

— the nature of the animal epithelia and outgrowths.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

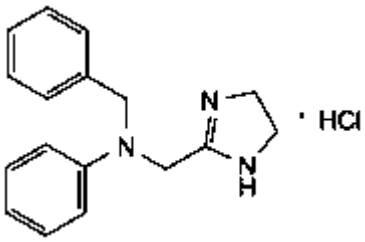
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Antazoline Hydrochloride

General Notices

(Ph. Eur. monograph 0972)



$C_{17}H_{20}ClN_3$ 301.8 *2508-72-7*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

Antazoline hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of *N*-benzyl-*N*-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]aniline hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, sparingly soluble in water, soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

It melts at about 240 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *antazoline hydrochloride CRS*. Examine the substances as discs prepared using *potassium chloride R*.

www.webofpharma.com

https://thuocngocanh.com/

B. Examine the chromatograms obtained in the test for related substances in daylight after spraying. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (b).

C. To 5 mL of solution S (see Tests) add, drop by drop, *dilute sodium hydroxide solution R* until an alkaline reaction is produced. Filter. The precipitate, washed with two quantities, each of 10 mL, of *water R* and dried in a desiccator under reduced pressure, melts (*2.2.14*) at 119 °C to 123 °C.

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* prepared from *distilled water R*, heating at 60 °C if necessary. Allow to cool and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of *methyl red solution R*. Not more than 0.1 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance. Heat the plate at 110 °C for 15 min before using.

Test solution (a) Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 5 mL with *methanol R*.

Reference solution (a) Dilute 0.5 mL of test solution (a) to 100 mL with *methanol R*.

Reference solution (b) Dissolve 20 mg of *antazoline hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (c) Dissolve 20 mg of *xylometazoline hydrochloride CRS* in 1 mL of test solution (a) and dilute to 5 mL with *methanol R*.

Apply to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture of 5 volumes of *diethylamine R*, 10 volumes of *methanol R* and 85 volumes of *ethyl acetate R*. Dry the plate in a current of warm air for 15 min. Examine in ultraviolet light at 254 nm. The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated principal spots. Spray with a mixture of equal volumes of a 200 g/L solution of *ferric chloride R* and a 5 g/L solution of *potassium ferricyanide R*. Examine immediately in daylight. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

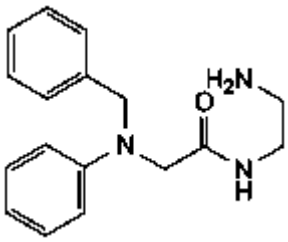
Not more than 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

Dissolve 0.250 g in 100 mL of *alcohol R*. Add 0.1 mL of *phenolphthalein solution R1*. Titrate with *0.1 M alcoholic potassium hydroxide*.

1 mL of *0.1 M alcoholic potassium hydroxide* is equivalent to 30.18 mg of $C_{17}H_{20}ClN_3$.

IMPURITIES



A. *N*-(2-aminoethyl)-2-(benzylphenylamino)acetamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

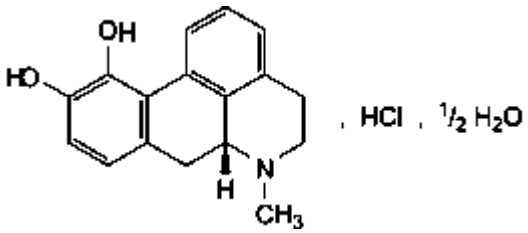
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Apomorphine Hydrochloride Hemihydrate

General Notices

(Ph. Eur. monograph 0136)



$C_{17}H_{18}ClNO_2,½H_2O$ 312.8 *41372-20-7*

Action and use

Dopamine receptor agonist; treatment of Parkinson's disease.

Preparation

Apomorphine Hydrochloride for Homoeopathic Preparations

Ph Eur

DEFINITION

(6a*R*)-6-Methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-10,11-diol hydrochloride hemihydrate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish-brown or green-tinged greyish, crystalline powder or crystals; on exposure to air and light, the green tinge becomes more pronounced.

Solubility

Sparingly soluble in water and in ethanol (96 per cent), practically insoluble in toluene.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 10.0 mg in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid solution. Dilute 10.0 mL of the solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Spectral range 230-350 nm

Absorption maximum At 273 nm.

Shoulder At 300-310 nm.

Specific absorbance at the absorption maximum 530 to 570.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *apomorphine hydrochloride hemihydrate CRS*.

C. To 5 mL of solution S (see Tests) add a few millilitres of *sodium hydrogen carbonate solution R* until a permanent, white precipitate is formed. The precipitate slowly becomes greenish. Add 0.25 mL of *0.05 M iodine* and shake. The precipitate becomes greyish-green. Collect the precipitate. The precipitate dissolves in *methylene chloride R* giving a violet-blue solution and in *ethanol (96 per cent) R* giving a blue solution.

D. To 2 mL of solution S (see Tests) add 0.1 mL of *nitric acid R*. Mix and filter. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.25 g without heating in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 or GY_5 (2.2.2, *Method II*).

pH (2.2.3)

4.0 to 5.0 for solution S.

Specific optical rotation (2.2.7)

-52 to -48 (dried substance).

Dissolve 0.25 g in a 2.06 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same acid solution.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in a 1 per cent *V/V* solution of *glacial acetic acid R* and dilute to 20.0 mL with the same solution.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with a 1 per cent *V/V* solution of *glacial acetic acid R*. Dilute 1.0 mL of this solution to 10.0 mL with a 1 per cent *V/V* solution of *glacial acetic acid R*.

Reference solution (b) Dissolve 12.5 mg of *apomorphine impurity B CRS* in a 1 per cent *V/V* solution of *glacial acetic acid R* and dilute to 10.0 mL with the same solution.

Reference solution (c) Dilute 2.0 mL of reference solution (b) to 10.0 mL with a 1 per cent *V/V* solution of *glacial acetic acid R*. Dilute 2.0 mL of this solution to 100.0 mL with a 1 per cent *V/V* solution of *glacial acetic acid R*.

Reference solution (d) Dissolve 25 mg of *boldine R* in a 1 per cent *V/V* solution of *glacial acetic acid R* and dilute to 10 mL with the same solution. To 1 mL of this solution add 1 mL of the test solution and dilute to 10 mL with a 1 per cent *V/V* solution of *glacial acetic acid R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 1.1 g/L solution of *sodium octanesulfonate R*, adjusted to pH 2.2 with a 50 per cent *m/m* solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 32	85 → 68	15 → 32
32 - 37	68	32

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to apomorphine (retention time = about 18 min): impurity B = about 0.4; boldine = about 0.9.

System suitability Reference solution (d):

— *resolution*: minimum 2.5 between the peaks due to boldine and apomorphine.

Calculation of percentage contents:

— for impurity B, use the concentration of impurity B in reference solution (c);

— for impurities other than B, use the concentration of apomorphine hydrochloride hemihydrate in reference solution (a).

Limits:

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

2.5 per cent to 4.2 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the first 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 30.38 mg of $C_{17}H_{18}ClNO_2$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

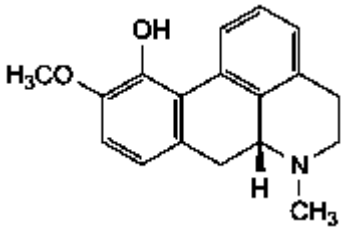
Specified impurities *B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

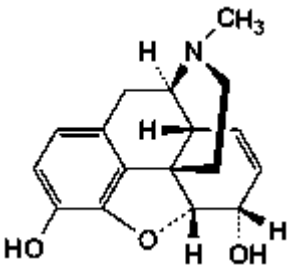
www.webofpharma.com

https://thuvienthuocngocanh.com/

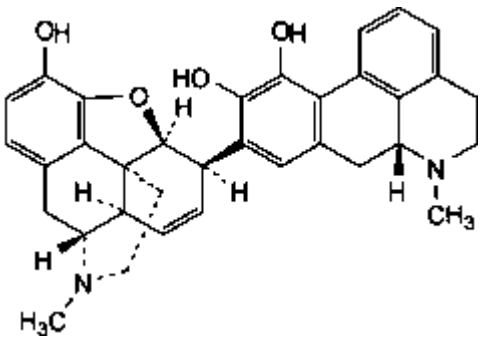
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C.



A. (6a*R*)-10-methoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinolin-11-ol (apocodeine),



B. 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol (morphine),



C. (6a*R*)-9-[7,8-didehydro-4,5α-epoxy-3-hydroxy-17-methylmorphinan-6α-yl]-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline-10,11-diol (morphine-apomorphine dimer).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

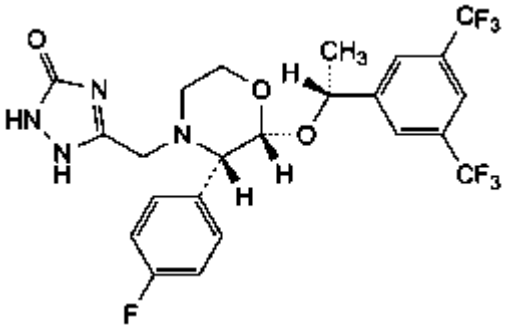
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aprepitant

General Notices

(Ph. Eur. monograph 2757)



$C_{23}H_{21}F_7N_4O_3$ 534.4 *170729-80-3*

Action and use

Neurokinin-1 (NK_1) receptor antagonist; prevention of nausea and vomiting associated with emetogenic chemotherapy.

Preparation

Aprepitant Capsules

Ph Eur

DEFINITION

5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)morpholin-4-yl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in heptane.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *aprepitant CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness on a water-bath and record new spectra using the residues.

TESTS

Specific optical rotation (2.2.7)

+ 66.0 to + 70.0 (anhydrous substance), measured at 25 °C.

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Solvent mixture *acetonitrile R1*, *water for chromatography R* (50:50 *V/V*).

Test solution Dissolve 40.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 40.0 mg of *aprepitant CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 4 mg of *aprepitant for system suitability CRS* (containing impurity A) in 5.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	65	35
2 - 22	65 → 20	35 → 80
22 - 32	20	80

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *aprepitant for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to aprepitant (retention time = about 15 min): impurity A = about 0.97.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity A and aprepitant.

Limits:

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)).

Water (2.5.32)

Maximum 0.2 per cent, determined on 0.200 g by direct sample introduction.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{23}H_{21}F_7N_4O_3$ taking into account the assigned content of *aprepitant CRS*.

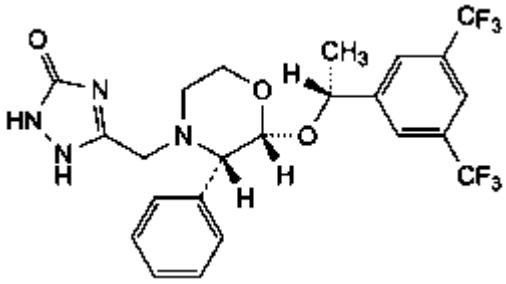
www.webofpharma.com

https://thuocngocanh.com/

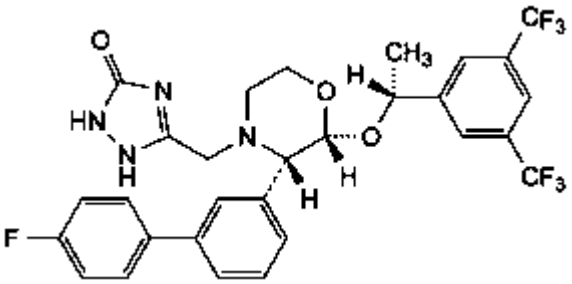
IMPURITIES

Specified impurities A.

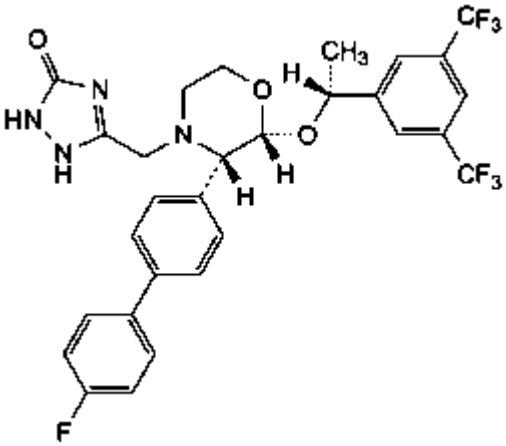
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.



A. 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-phenylmorpholin-4-yl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one,



B. 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4′-fluorobiphenyl-3-yl)morpholin-4-yl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one,



C. 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4′-fluorobiphenyl-4-yl)morpholin-4-yl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products
Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aprepitant Capsules

General Notices

Action and use

Neurokinin-1 (NK_1) receptor antagonist; prevention of nausea and vomiting associated with emetogenic chemotherapy.

DEFINITION

Aprepitant Capsules contain Aprepitant.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of aprepitant, $C_{23}H_{21}F_7N_4O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the capsule contents containing 0.1 g of Aprepitant in 75 mL of *methanol*, mix with the aid of ultrasound and filter (a 0.45-µm nylon-66 filter is suitable). Dilute to 100 mL with *methanol*. Dilute 1 volume of this solution to 10 volumes with *methanol*. The *light absorption*, Appendix II B, in the range 200 to 400 nm, exhibits 3 maxima, at 211, 264 and 270 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 900 mL of a 2.2% w/v solution of *sodium dodecyl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 20 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted, if necessary, with sufficient of a 2.2% w/v solution of *sodium dodecyl sulfate* to produce a solution expected to contain 0.0044% w/v of Aprepitant.

(2) 0.0044% w/v of *aprepitant BPCRS* prepared by dissolving an appropriate amount of *aprepitant BPCRS* in the minimum volume of *methanol* and diluting with a sufficient volume of a 2.2% w/v solution of *sodium dodecyl sulfate*.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx-C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Equal volumes of a 0.1% v/v solution of *orthophosphoric acid* and *acetonitrile R1*.

DETERMINATION OF CONTENT

Calculate the total content of aprepitant, $C_{23}H_{21}F_7N_4O_3$, in the medium from the chromatograms obtained and using the declared content of $C_{23}H_{21}F_7N_4O_3$ in *aprepitant BPCRS*.

LIMITS

The amount of aprepitant released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a solution containing equal volumes of *acetonitrile R1* and a 0.1% v/v solution of *orthophosphoric acid* (solution A).

(1) Dissolve a quantity of the contents of the capsules containing 0.12 g of Aprepitant in 150 mL of solution A and mix with the aid of ultrasound. Dilute to 200 mL with solution A, mix and filter (a 0.45-µm Nylon 66 syringe filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A. Dilute 1 volume of this solution to 5 volumes with solution A.
(3) 0.06% w/v of *aprepitant impurity standard BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (XTerra RP-18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile R1* and 95 volumes of a 0.1% v/v solution of *orthophosphoric acid*.

Mobile phase B 5 volumes of a 0.1% v/v solution of *orthophosphoric acid* and 95 volumes of *acetonitrile R1*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	60→58	40→42	linear gradient
20-25	58→35	42→65	linear gradient
25-33	35	65	Isocratic
33-33.1	35→60	65→40	linear gradient
33.1-40	60	40	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to aprepitant (retention time about 15 minutes) are: impurity A, about 0.85 and aprepitant impurity 1 and 2, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and aprepitant is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any peak corresponding to impurity 1 and 2 is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a solution containing 2 volumes of *acetonitrile* and 3 volumes of *water* (solution B).

(1) Shake a quantity of the mixed contents of 20 capsules containing 0.4 g of Aprepitant in solution B. Add sufficient *acetonitrile* to produce a solution containing 0.08% w/v of Aprepitant and filter (0.45-µm PTFE is suitable). Dilute 8 volumes of this solution to 25 volumes with mobile phase.

(2) 0.025% w/v of *aprepitant BPCRS* in the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

9 volumes of *acetonitrile R1* and 11 volumes of a 0.34% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 using *orthophosphoric acid*.

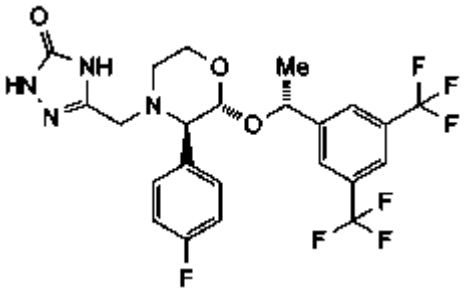
DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{21}F_7N_4O_3$ in the capsules using the declared content of $C_{23}H_{21}F_7N_4O_3$ in *aprepitant BPCRS*.

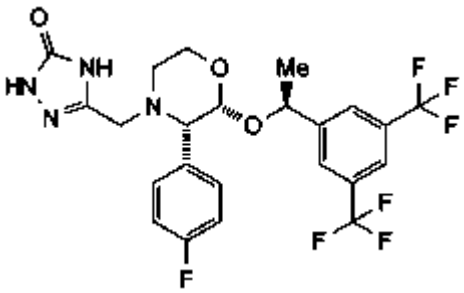
IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aprepitant and:

1. 5-{[(2*R*,3*R*)-2-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)morpholin-4-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (*R,R,R*-diastereoisomer)



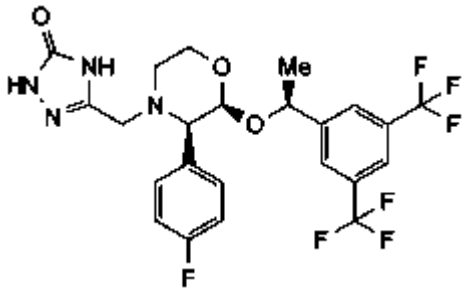
2. 5-{[(2*R*,3*S*)-2-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)morpholin-4-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (*R*,*S*,*S*-diastereoisomer)



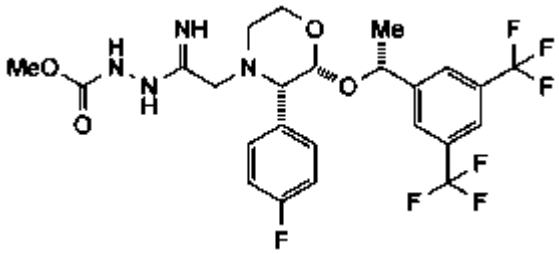
3. 5-{[(2*S*,3*R*)-2-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)morpholin-4-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (*S*,*R*,*S*-enantiomer)

www.webofpharma.com

https://thuocngocanh.com/



4. methyl 2-{2-[(2*R*,3*S*)-2-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)morpholin-4-yl]-1-iminoethyl}hydrazine-1-carboxylate



© Crown Copyright 2022

www.webofpharma.com

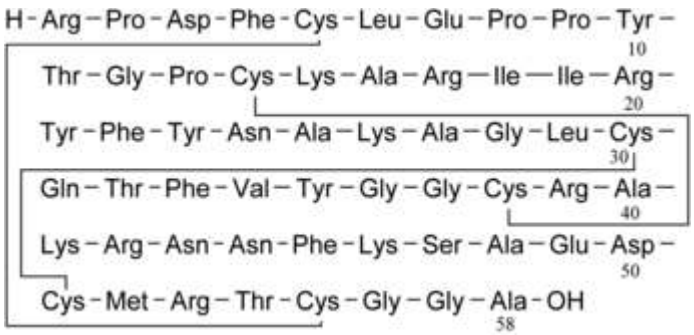
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aprotinin

General Notices

(Ph. Eur. monograph 0580)



$C_{284}H_{432}N_{84}O_{79}S_7$ 6511 *9087-70-1*

Action and use

Antifibrinolytic.

Ph Eur

DEFINITION

Aprotinin is a polypeptide consisting of a chain of 58 amino acids. It inhibits stoichiometrically the activity of several proteolytic enzymes such as chymotrypsin, kallikrein, plasmin and trypsin. It contains not less than 3.0 Ph. Eur. U. of aprotinin activity per milligram, calculated with reference to the dried substance.

PRODUCTION

The animals from which aprotinin is derived must fulfil the requirements for the health of animals suitable for human consumption.

The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

Histamine (*2.6.10*)

Maximum 0.2 µg of histamine base per 3 Ph. Eur. U.

CHARACTERS

Appearance

Almost white hygroscopic powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Soluble in water and in isotonic solutions, practically insoluble in organic solvents.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Solution S (see Tests).

Reference solution Dilute *aprotinin solution BRP* in *water R* to obtain a concentration of 15 Ph. Eur. U./mL.

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *glacial acetic acid R* (80:100 *V/V*) containing 100 g/L of *sodium acetate R*.

Application 10 µL.

Development Over a path of 12 cm.

Drying In air.

Detection Spray with a solution of 0.1 g of *ninhydrin R* in a mixture of 6 mL of a 10 g/L solution of *cupric chloride R*, 21 mL of *glacial acetic acid R* and 70 mL of *anhydrous ethanol R*. Dry the plate at 60 °C.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Determine the ability of the substance to be examined to inhibit trypsin activity using the method described below.

Test solution Dilute 1 mL of solution S to 50 mL with *buffer solution pH 7.2 R*.

Trypsin solution Dissolve 10 mg of *trypsin for aprotinin assay BRP* in *0.002 M hydrochloric acid* and dilute to 100 mL with the same acid.

Casein solution Dissolve 0.2 g of *casein R* in *buffer solution pH 7.2 R* and dilute to 100 mL with the same buffer solution.

Precipitating solution *glacial acetic acid R*, *water R*, *anhydrous ethanol R* (1:49:50 *V/V/V*).

Mix 1 mL of the test solution with 1 mL of the trypsin solution. Allow to stand for 10 min and add 1 mL of the casein solution. Incubate at 35 °C for 30 min. Cool in iced water and add 0.5 mL of the precipitating solution. Shake and allow to stand at room temperature for 15 min. The solution is cloudy. Carry out a blank test under the same conditions using *buffer solution pH 7.2 R* instead of the test solution. The solution is not cloudy.

TESTS

Solution S

Prepare a solution of the substance to be examined containing 15 Ph. Eur. U./mL, calculated from the activity stated on the label.

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is clear (*2.2.1*).

Absorbance (*2.2.25*)

Maximum 0.80 by measuring at the absorption maximum at 277 nm.

Prepare a solution of the substance to be examined containing 3.0 Ph. Eur. U./mL.

Des-Ala-aprotinin and des-Ala-des-Gly-aprotinin

Capillary zone electrophoresis (*2.2.47*): use the normalisation procedure.

Test solution Prepare a solution of the substance to be examined in *water R* containing not less than 1 Ph. Eur. U./mL.

Reference solution Dilute *aprotinin solution BRP* in *water R* to obtain the same concentration as the test solution.

Capillary:

— *material*: uncoated fused silica;

— *size*: effective length = 45-60 cm, Ø = 75 µm.

Temperature 25 °C.

CZE buffer Dissolve 8.21 g of *potassium dihydrogen phosphate R* in 400 mL of *water R*, adjust to pH 3.0 with *phosphoric acid R*, dilute to 500.0 mL with *water R* and filter through a membrane filter (nominal pore size 0.45 µm).

Detection Spectrophotometer at 214 nm.

Between-run rinsing Rinse the capillary for at least 1 min with *0.1 M sodium hydroxide* filtered through a membrane filter (nominal pore size 0.45 µm) and for 2 min with the CZE buffer.

Injection Under pressure or vacuum (for example, 3 s at a differential pressure of 3.5 kPa).

Migration Apply a field strength of 0.2 kV/cm, using the CZE buffer as the electrolyte in both buffer reservoirs.

Run time 30 min.

Identification of impurities Use the electropherogram supplied with *aprotinin solution BRP* and the electropherogram obtained with the reference solution to identify the peaks due to impurities A and B.

Relative migration With reference to aprotinin (migration time = about 22 min): impurity A = about 0.98; impurity B = about 0.99.

System suitability Reference solution after at least 6 injections:

— *migration time*: aprotinin = 19.0 min to 25.0 min;

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 0.8 between the peaks due to impurities A and B; minimum 0.5 between the peaks due to impurity B and aprotinin;

— *peak distribution*: the electropherogram obtained is qualitatively and quantitatively similar to the electropherogram supplied with *aprotinin solution BRP*;

— *height of the principal peak*: at least 1000 times the height of the baseline noise. If necessary, adjust the sample load to give peaks of sufficient height.

Limits:

— *impurity A*: maximum 8.0 per cent;

— *impurity B*: maximum 7.5 per cent.

Pyroglutamyl-aprotinin and related compounds

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Prepare a solution of the substance to be examined in mobile phase A, containing about 5 Ph. Eur. U./mL.

Reference solution Dissolve the contents of a vial of *aprotinin for system suitability CRS* in 2.0 mL of mobile phase A.

Column:

— *size*: *l* = 0.075 m, Ø = 7.5 mm;

— *stationary phase*: *strong cation-exchange silica gel for chromatography R* (10 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.52 g of *potassium dihydrogen phosphate R* and 7.26 g of *disodium hydrogen phosphate dihydrate R* in 1000 mL of *water for chromatography R*; filter and degas;

— *mobile phase B*: dissolve 3.52 g of *potassium dihydrogen phosphate R*, 7.26 g of *disodium hydrogen phosphate dihydrate R* and 66.07 g of *ammonium sulfate R* in 1000 mL of *water for chromatography R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 21	92 → 64	8 → 36
21 - 30	64 → 0	36 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 40 µL.

Relative retention With reference to aprotinin (retention time = 17.0 min to 20.0 min): impurity C = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to impurity C and aprotinin;

— *symmetry factor*: maximum 1.3 for the peak due to aprotinin.

Limits:

— *impurity C*: maximum 1.0 per cent;

— *any other impurity*: maximum 0.5 per cent;

— *sum of impurities other than C*: maximum 1.0 per cent.

Aprotinin oligomers

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution Prepare a solution of the substance to be examined in *water R* containing about 5 Ph. Eur. U./mL.

Reference solution Treat the substance to be examined to obtain about 2 per cent aprotinin oligomers. For example, heat freeze-dried aprotinin at about 110 °C for about 4 h. Then dissolve in *water R* to obtain a concentration of about 5 Ph. Eur. U./mL.

Column 3 columns coupled in series:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 20 000 to 10 000 000 (8 µm).

Mobile phase *acetonitrile R*, *glacial acetic acid R*, *water for chromatography R* (2:2:6 *V/V/V*); filter and degas.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 277 nm.

Injection 100 µL.

Run time 40 min.

Relative retention With reference to aprotinin monomer (retention time = 24.5 min to 25.5 min): aprotinin dimer = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 1.3 between the peaks due to aprotinin dimer and monomer;

www.webofpharma.com

https://thuocngocanh.com/

— *symmetry factor*: maximum 2.5 for the peak due to aprotinin monomer.

Limit:

— *total*: maximum 1.0 per cent.

Loss on drying (*2.2.32*)

Maximum 6.0 per cent, determined on 0.100 g by drying *in vacuo*.

Bacterial endotoxins (*2.6.14*)

Less than 0.14 IU per European Pharmacopoeia Unit of aprotinin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

The activity of aprotinin is determined by measuring its inhibitory action on a solution of trypsin of known activity. The inhibiting activity of the aprotinin is calculated from the difference between the initial activity and the residual activity of the trypsin.

The inhibiting activity of aprotinin is expressed in European Pharmacopoeia Units. 1 Ph. Eur. U. inhibits 50 per cent of the enzymatic activity of 2 microkatals of trypsin.

Use a reaction vessel with a capacity of about 30 mL, provided with:

— a device that will maintain a temperature of 25 ± 0.1 °C;

— a stirring device, such as a magnetic stirrer;

— a lid with 5 holes for accommodating the electrodes, the tip of a burette, a tube for the admission of nitrogen and the introduction of the reagents.

An automatic or manual titration apparatus may be used. In the latter case the burette is graduated in 0.05 mL and the pH-meter is provided with a wide reading scale and glass-silver-silver chloride or other suitable electrodes.

Test solution Prepare a solution of the substance to be examined in *0.0015 M borate buffer solution pH 8.0 R* expected to contain 1.67 Ph. Eur. U./mL (about 0.6 mg (*m* mg) per millilitre).

Trypsin solution Prepare a solution of *trypsin for aprotinin assay BRP* containing about 0.8 microkatals per millilitre, using *0.001 M hydrochloric acid* as the solvent. Use a freshly prepared solution and keep in iced water.

Trypsin and aprotinin solution To 4.0 mL of the trypsin solution add 1.0 mL of the test solution. Dilute immediately to 40.0 mL with *0.0015 M borate buffer solution pH 8.0 R*. Allow to stand at room temperature for 10 min and then keep in iced water. Use within 6 h of preparation.

Dilute trypsin solution Dilute 0.5 mL of the trypsin solution to 10.0 mL with *0.0015 M borate buffer solution pH 8.0 R*. Allow to stand at room temperature for 10 min and then keep in iced water.

www.webofpharma.com

https://thuocngocanh.com/

Maintain an atmosphere of nitrogen in the reaction flask and stir continuously; introduce 9.0 mL of *0.0015 M borate buffer solution pH 8.0 R* and 1.0 mL of a freshly prepared 6.9 g/L solution of *benzoylarginine ethyl ester hydrochloride R*. Adjust to pH 8.0 with *0.1 M sodium hydroxide*. When the temperature has reached equilibrium at 25 ± 0.1 °C, add 1.0 mL of the trypsin and aprotinin solution and start a timer. Maintain at pH 8.0 by the addition of *0.1 M sodium hydroxide* and note the volume added every 30 s. Continue the reaction for 6 min. Determine the number of millilitres of *0.1 M sodium hydroxide* used per second (n_1 mL). Carry out, under the same conditions, a titration using 1.0 mL of the dilute trypsin solution. Determine the number of millilitres of *0.1 M sodium hydroxide* used per second (n_2 mL).

Calculate the aprotinin activity in European Pharmacopoeia Units per milligram using the following expression:

$$\frac{4000\left(2n_2 - n_1\right)}{m}$$

The estimated activity is not less than 90 per cent and not more than 110 per cent of the activity stated on the label.

STORAGE

In an airtight, tamper-evident container, protected from light.

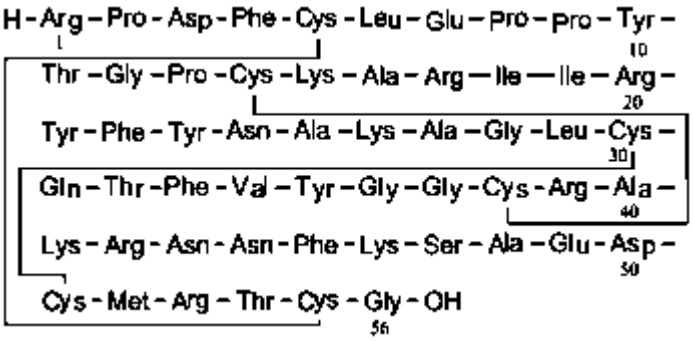
LABELLING

The label states:

— the number of European Pharmacopoeia Units of aprotinin activity per milligram;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

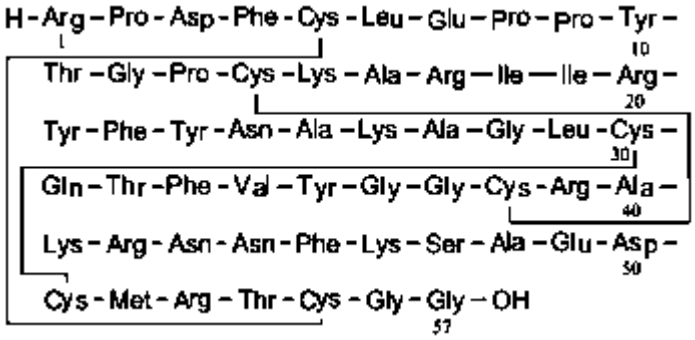
IMPURITIES



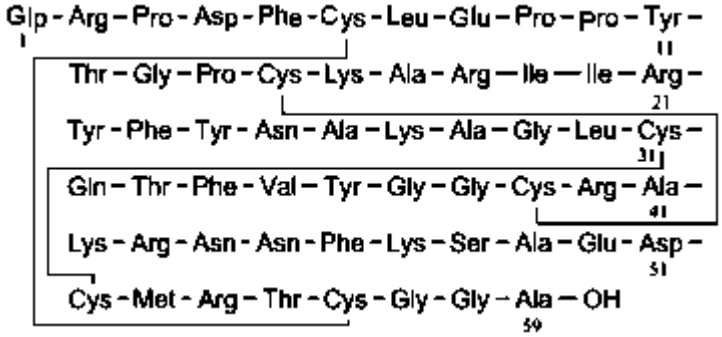
A. aprotinin-(1-56)-peptide,

www.webofpharma.com

https://thuocngocanh.com/



B. aprotinin-(1-57)-peptide,



C. (5-oxoprolyl)aprotinin (pyroglutamylaprotinin).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aprotinin Concentrated Solution

General Notices

(Ph. Eur. monograph 0579)

```
RPDFCLEPPY  TGPCKARIIR  YFYNAKAGLC  QTFVYGGCRA  40
KRNNFKSAED  CMRTCGGA                            58
```

disulfide bridges: 5-55, 14-38, 30-51.

$C_{284}H_{432}N_{84}O_{79}S_7$ 6512

Action and use

Antifibrinolytic.

Ph Eur

DEFINITION

Aprotinin concentrated solution is a solution of aprotinin, a polypeptide consisting of a chain of 58 amino acids, which inhibits stoichiometrically the activity of several proteolytic enzymes such as chymotrypsin, kallikrein, plasmin and trypsin. It contains not less than 15.0 Ph. Eur. U. of aprotinin activity per millilitre.

PRODUCTION

The animals from which aprotinin is derived must fulfil the requirements for the health of animals suitable for human consumption.

The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

Histamine (*2.6.10*)

Maximum 0.2 µg of histamine base per 3 Ph. Eur. U.

CHARACTERS

Appearance

Clear, colourless liquid.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

www.webofpharma.com

https://thietbiuocngocanh.com/

Test solution Solution S (see Tests).

Reference solution Dilute *aprotinin solution BRP* in *water R* to obtain a concentration of 15 Ph. Eur. U./mL.

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *glacial acetic acid R* (80:100 *V/V*) containing 100 g/L of *sodium acetate R*.

Application 10 µL.

Development Over a path of 12 cm.

Drying In air.

Detection Spray with a solution of 0.1 g of *ninhydrin R* in a mixture of 6 mL of a 10 g/L solution of *cupric chloride R*, 21 mL of *glacial acetic acid R* and 70 mL of *anhydrous ethanol R*. Dry the plate at 60 °C.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Determine the ability of the preparation to be examined to inhibit trypsin activity using the method described below.

Test solution Dilute 1 mL of solution S to 50 mL with *buffer solution pH 7.2 R*.

Trypsin solution Dissolve 10 mg of *trypsin for aprotinin assay BRP* in *0.002 M hydrochloric acid* and dilute to 100 mL with the same acid.

Casein solution Dissolve 0.2 g of *casein R* in *buffer solution pH 7.2 R* and dilute to 100 mL with the same buffer solution.

Precipitating solution *glacial acetic acid R*, *water R*, *anhydrous ethanol R* (1:49:50 *V/V/V*).

Mix 1 mL of the test solution with 1 mL of the trypsin solution. Allow to stand for 10 min and add 1 mL of the casein solution. Incubate at 35 °C for 30 min. Cool in iced water and add 0.5 mL of the precipitating solution. Shake and allow to stand at room temperature for 15 min. The solution is cloudy. Carry out a blank test under the same conditions using *buffer solution pH 7.2 R* instead of the test solution. The solution is not cloudy.

TESTS

Solution S

Prepare a solution containing 15 Ph. Eur. U./mL, if necessary by dilution, on the basis of the activity stated on the label.

Appearance of solution

Solution S is clear (*2.2.1*).

Absorbance (*2.2.25*)

Maximum 0.80 by measuring at the absorption maximum at 277 nm.

Prepare a solution containing 3.0 Ph. Eur. U./mL.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dilute the preparation to be examined in water R to a concentration of about 5 Ph. Eur. U./mL.

Reference solution (a) Dilute aprotinin solution BRP in water R to obtain the same concentration as the test solution.

Reference solution (b) Dilute 0.1 mL of reference solution (a) to 100.0 mL with water R.

Column:

— *size*: *l* = 0.10 m, Ø = 3.0 mm;

— *stationary phase*: end-capped solid core pentafluorophenylpropylsilyl silica gel for chromatography R (2.7 µm);

— *temperature*: 5 °C.

Mobile phase:

— *mobile phase A*: mix 6.3 mL of phosphoric acid R with 600 mL of water for chromatography R and dilute to 900 mL with the same solvent. Adjust to pH 2.2 with a solution of potassium hydroxide R (56.1 g/L) and dilute to 1000 mL with water for chromatography R. Filter through a membrane filter (nominal pore size 0.22 µm);

— *mobile phase B*: acetonitrile R1;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 7	90 → 84.5	10 → 15.5
7 - 12	84.5 → 81	15.5 → 19
12 - 13	81	19

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 215 nm.

Autosampler Set at 5 °C.

Injection 5 µL.

Identification of peaks Use the chromatogram supplied with aprotinin solution BRP and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, D, E, F, G, H and I.

Relative retention With reference to aprotinin (retention time = about 7 min): impurity D = about 0.47; impurity F = about 0.53; impurities E and G = about 0.66; impurity H = about 0.71; impurity I = about 0.77; impurity A = about 0.90; impurity B = about 0.95.

www.webofpharma.com

https://thuocngocanh.com/

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities A and B; minimum 1.5 between the peak due to impurity B and the principal peak in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *impurity A*: maximum 7.7 per cent;

— *impurity B*: maximum 6.6 per cent;

— *impurity I*: maximum 5.8 per cent;

— *sum of impurities E and G*: maximum 4.2 per cent;

— *impurity H*: maximum 0.9 per cent;

— *impurity D*: maximum 0.7 per cent;

— *impurity F*: maximum 0.4 per cent;

— *unspecified impurities*: for each impurity, maximum 1.0 per cent;

— *total*: maximum 27.4 per cent;

— *reporting threshold*: 0.2 per cent.

Pyroglutamyl-aprotinin and related compounds

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dilute the preparation to be examined in mobile phase A to a concentration of about 5 Ph. Eur. U./mL.

Reference solution Dilute *aprotinin solution BRP* in mobile phase A to obtain the same concentration as the test solution.

Column:

— *size*: *l* = 0.075 m, Ø = 7.5 mm;

— *stationary phase*: *strong cation-exchange silica gel for chromatography R* (10 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.52 g of *potassium dihydrogen phosphate R* and 7.26 g of *disodium hydrogen phosphate dihydrate R* in 1000 mL of *water for chromatography R*; filter and degas;

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: dissolve 3.52 g of *potassium dihydrogen phosphate R*, 7.26 g of *disodium hydrogen phosphate dihydrate R* and 66.07 g of *ammonium sulfate R* in 1000 mL of *water for chromatography R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 21	92 → 64	8 → 36
21 - 30	64 → 0	36 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 40 µL.

Identification of peaks Use the chromatogram supplied with *aprotinin solution BRP* and the chromatogram obtained with the reference solution to identify the peaks due to impurities C and J.

Relative retention With reference to aprotinin (retention time = 17.0 min to 20.0 min): impurity J = about 0.8; impurity C = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to impurity C and aprotinin;

— *symmetry factor*: 0.7 to 1.3 for the peak due to aprotinin.

Limits:

— *impurity C*: maximum 1.0 per cent;

— *impurity J*: maximum 0.7 per cent;

— *any other impurity*: maximum 0.5 per cent;

— *sum of impurities other than C*: maximum 1.0 per cent;

— *reporting threshold*: 0.25 per cent.

Aprotinin oligomers

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution Dilute the preparation to be examined in *water R* to obtain a concentration of about 5 Ph. Eur. U./mL.

Reference solution Treat the substance to be examined to obtain about 2 per cent aprotinin oligomers. For example, heat freeze-dried aprotinin at about 110 °C for about 4 h. Then dissolve in *water R* to obtain a concentration of about 5 Ph. Eur. U./mL.

Column 3 columns coupled in series:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 20 000 to 10 000 000 (8 µm).

Mobile phase *acetonitrile R*, *glacial acetic acid R*, *water for chromatography R* (20:20:60 *V/V/V*); filter and degas.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 277 nm.

Injection 100 µL.

Run time 40 min.

Relative retention With reference to aprotinin monomer (retention time = 24.5 min to 25.5 min): aprotinin dimer = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 1.3 between the peaks due to aprotinin dimer and monomer;

— *symmetry factor*: maximum 2.5 for the peak due to aprotinin monomer.

Limit:

— *total*: maximum 1.0 per cent.

Specific activity of the dry residue

Minimum 3.0 Ph. Eur. U. of aprotinin activity per milligram of dry residue.

Evaporate 25.0 mL to dryness in a water-bath, dry the residue at 110 °C for 15 h and weigh. From the mass of the residue and the activity determined as described below, calculate the number of European Pharmacopoeia Units per milligram of dry residue.

Bacterial endotoxins (*2.6.14*)

Less than 0.14 IU per European Pharmacopoeia Unit of aprotinin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

The activity of aprotinin is determined by measuring its inhibitory action on a solution of trypsin of known activity. The inhibiting activity of the aprotinin is calculated from the difference between the initial activity and the residual activity of the trypsin.

The inhibiting activity of aprotinin is expressed in European Pharmacopoeia Units. 1 Ph. Eur. U. inhibits 50 per cent of the enzymatic activity of 2 microkatals of trypsin.

Use a reaction vessel with a capacity of about 30 mL, provided with:

— a device that will maintain a temperature of 25 ± 0.1 °C;

www.webofpharma.com

https://thuocngocanh.com/

— a stirring device, such as a magnetic stirrer;

— a lid with 5 holes for accommodating the electrodes, the tip of a burette, a tube for the admission of nitrogen and the introduction of the reagents.

An automatic or manual titration apparatus may be used. In the latter case the burette is graduated in 0.05 mL and the pH-meter is provided with a wide reading scale and glass-silver-silver chloride or other suitable electrodes.

Test solution With *0.0015 M borate buffer solution pH 8.0 R* prepare an appropriate dilution (*D*) of the aprotinin concentrated solution expected, on the basis of the stated potency, to contain 1.67 Ph. Eur. U./mL.

Trypsin solution Prepare a solution of *trypsin for aprotinin assay BRP* containing about 0.8 microkatals per millilitre using *0.001 M hydrochloric acid* as the solvent. Use a freshly prepared solution and keep in iced water.

Trypsin and aprotinin solution To 4.0 mL of the trypsin solution add 1.0 mL of the test solution. Dilute immediately to 40.0 mL with *0.0015 M borate buffer solution pH 8.0 R*. Allow to stand at room temperature for 10 min and then keep in iced water. Use within 6 h of preparation.

Dilute trypsin solution Dilute 0.5 mL of the trypsin solution to 10.0 mL with *0.0015 M borate buffer solution pH 8.0 R*. Allow to stand at room temperature for 10 min and then keep in iced water.

Maintain an atmosphere of nitrogen in the reaction flask and stir continuously; introduce 9.0 mL of *0.0015 M borate buffer solution pH 8.0 R* and 1.0 mL of a freshly prepared 6.9 g/L solution of *benzoylarginine ethyl ester hydrochloride R*. Adjust to pH 8.0 with *0.1 M sodium hydroxide*. When the temperature has reached equilibrium at 25 ± 0.1 °C, add 1.0 mL of the trypsin and aprotinin solution and start a timer. Maintain at pH 8.0 by the addition of *0.1 M sodium hydroxide* and note the volume added every 30 s. Continue the reaction for 6 min. Determine the number of millilitres of *0.1 M sodium hydroxide* used per second (n_1 mL). Carry out, under the same conditions, a titration using 1.0 mL of the dilute trypsin solution. Determine the number of millilitres of *0.1 M sodium hydroxide* used per second (n_2 mL).

Calculate the aprotinin activity in European Pharmacopoeia Units per millilitre using the following expression:

$$4000\left(2n_2 - n_1\right) \times D$$

D = dilution factor of the aprotinin concentrated solution to be examined in order to obtain a solution containing 1.67 Ph. Eur. U./mL.

The estimated activity is not less than 90 per cent and not more than 110 per cent of the activity stated on the label.

STORAGE

In an airtight, tamper-evident container, protected from light.

LABELLING

The label states:

— the number of European Pharmacopoeia Units of aprotinin activity per millilitre;

www.webofpharma.com

https://thuocngocanh.com/

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

```
RPDFCLEPPY  TGPCKARIIR  YFYNAKAGLC  QTFVYGGCRA  40
KRNNFKSAED  CMRTCG                              56
```

disulfide bridges: 5-55, 14-38, 30-51.

A. aprotinin-(1-56)-peptide (des-Gly^{57},Ala^{58}-aprotinin),

```
RPDFCLEPPY  TGPCKARIIR  YFYNAKAGLC  QTFVYGGCRA  40
KRNNFKSAED  CMRTCGG                             57
```

disulfide bridges: 5-55, 14-38, 30-51.

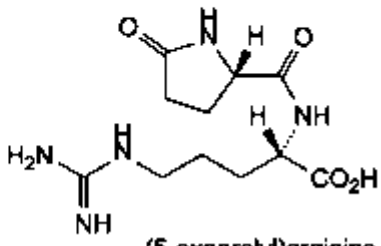
B. aprotinin-(1-57)-peptide (des-Ala^{58}-aprotinin),

```
RPDFCLEPPY  TGPCKARIIR  YFYNAKAGLC  QTFVYGGCRA  40
KRNNFKSAED  CMRTCGGA                            58
```

disulfide bridges: 5-55, 14-38, 30-51.

modified residue:

R
1



(5-oxoprolyl)arginine

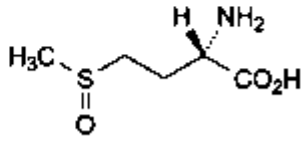
C. (5-oxoprolyl)aprotinin (pyroglutamylaprotinin), Glp-aprotinin),

```
RPDFCLEPPY  TGPCKARIIR  YFYNAKAGLC  QTFVYGGCRA  40
KRNNFKSAED  CMRTCG                              56
```

disulfide bridges: 5-55, 14-38, 30-51.

modified residue:

M
52



L-methionine (*RS*)-*S*-oxide

D. epimer 1 of [52-methionine (*RS*)-*S*-oxide]aprotinin-(1-56)-peptide (des-Gly^{57},Ala^{58}-[(*R*)-*S*-oxo-L-Met^{52}]aprotinin or des-Gly^{57},Ala^{58}-[(*S*)-*S*-oxo-L-Met^{52}]aprotinin),

E. epimer 2 of [52-methionine (*RS*)-*S*-oxide]aprotinin-(1-56)-peptide (des-Gly^{57},Ala^{58}-[(*R*)-*S*-oxo-L-Met^{52}]aprotinin or des-Gly^{57},Ala^{58}-[(*S*)-*S*-oxo-L-Met^{52}]aprotinin),

www.webofpharma.com

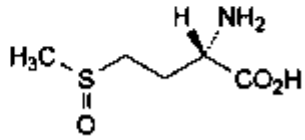
https://thuocngocanh.com/

```
RPDFCLEPPY  TGPCKARIIR  YFYNAKAGLC  QTFVYGGCRA  40
KRNNFKSAED  CMRTCGG                             57
```

disulfide bridges: 5-55, 14-38, 30-51.

modified residue:

M
52



L-methionine (*RS*)-*S*-oxide

F. epimer 1 of [52-methionine (*RS*)-*S*-oxide]aprotinin-(1-57)-peptide (des-Ala^{58}-[(*R*)-*S*-oxo-L-Met^{52}]aprotinin or des-Ala^{58}-[(*S*)-*S*-oxo-L-Met^{52}]aprotinin),

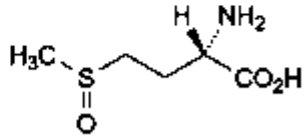
G. epimer 2 of [52-methionine (*RS*)-*S*-oxide]aprotinin-(1-57)-peptide (des-Ala^{58}-[(*R*)-*S*-oxo-L-Met^{52}]aprotinin or des-Ala^{58}-[(*S*)-*S*-oxo-L-Met^{52}]aprotinin),

```
RPDFCLEPPY  TGPCKARIIR  YFYNAKAGLC  QTFVYGGCRA  40
KRNNFKSAED  CMRTCGGA                            58
```

disulfide bridges: 5-55, 14-38, 30-51.

modified residue:

M
52



L-methionine (*RS*)-*S*-oxide

H. epimer 1 of [52-methionine (*RS*)-*S*-oxide]aprotinin ([(*R*)-*S*-oxo-L-Met^{52}]aprotinin or [(*S*)-*S*-oxo-L-Met^{52}]aprotinin),

I. epimer 2 of [52-methionine (*RS*)-*S*-oxide]aprotinin ([(*R*)-*S*-oxo-L-Met^{52}]aprotinin or [(*S*)-*S*-oxo-L-Met^{52}]aprotinin),

```
RPDFCLEPPY  TGPCKARIIR  YFYNAKAGLC  ETFVYGGCRA  40
KRNNFKSAED  CMRTCGGA                            58
```

disulfide bridges: 5-55, 14-38, 30-51.

J. [31-glutamic acid]aprotinin ([Glu^{31}]aprotinin).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aqueous Calamine Cream

General Notices

DEFINITION

Aqueous Calamine Cream contains 4% w/w of Calamine and 3% w/w of Zinc Oxide in a suitable oil-in-water emulsified basis.

Extemporaneous preparation

The following formula and directions apply.

Calamine	40 g
Zinc Oxide	30 g
Liquid Paraffin	200 g
Self-emulsifying Glyceryl Monostearate	50 g
Cetomacrogol Emulsifying Wax	50 g
Phenoxyethanol	5 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 g

Melt the Cetomacrogol Emulsifying Wax with the Self-emulsifying Glyceryl Monostearate, add the Liquid Paraffin and heat to about 60°. Dissolve the Phenoxyethanol in about 620 g of Purified Water at about 60°, add the oily phase to the phenoxyethanol solution and mix. Stir until cool, add sufficient Purified Water to produce 930 g and mix. Triturate the Calamine and the Zinc Oxide and incorporate in the cream.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc, Zn

4.3 to 5.2% w/w.

IDENTIFICATION

The residue obtained in the Assay is yellow when hot and white when cool.

ASSAY

Gently heat 4 g, taking precautions to avoid loss caused by spitting, until the basis is completely volatilised or charred, increase the temperature until the carbon is removed and ignite the residue to constant weight. Each g of residue is equivalent to 0.8034 g of Zn.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aqueous Cream

General Notices

DEFINITION

Emulsifying Ointment	300 g
Phenoxyethanol	10 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 g

The suitability of the Cream for use as a diluent should be confirmed before use.

PRODUCTION

As stated in the General Notice on Antimicrobial Preservatives, a suitable alternative antimicrobial preservative may be substituted provided that the identity and concentration are stated on the label.

Extemporaneous preparation

The following directions apply.

Dissolve the Phenoxyethanol in sufficient Purified Water at about 60° to produce a total weight of about 700 g. Melt the Emulsifying Ointment, add the phenoxyethanol solution when both are at about 60° and mix. Stir gently until cool, add sufficient of the Purified Water to produce 1000 g and mix.

The cream complies with the requirements stated under Topical Semi-solid Preparations.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Loading [MathJax]/jax/output/HTML-CSS/fonts/TeX/fontdata.js

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aqueous Iodine Oral Solution

General Notices

DEFINITION

Iodine	50 g
Potassium Iodide	100 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

Extemporaneous preparation

The following directions apply.

Dissolve the Potassium Iodide and the Iodine in 100 mL of the Purified Water and add sufficient of the Purified Water to produce 1000 mL.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of iodine, I

4.75 to 5.25% w/v.

Content of potassium iodide, KI

9.5 to 10.5% w/v.

ASSAY

Dilute 25 mL to 100 mL with *water*.

For iodine

To 20 mL of the diluted solution add 10 mL of *water* and titrate with 0.1M *sodium thiosulfate VS*. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 12.69 mg of I.

For potassium iodide

To 10 mL of the diluted solution add 20 mL of *water* and 40 mL of *hydrochloric acid* and titrate with *0.05M potassium iodate VS* until the dark brown solution which is produced becomes pale brown. Add 1 mL of *amaranth solution* and continue the titration until the red colour just changes to pale yellow. From the number of mL of *0.05M potassium iodate VS* required subtract one quarter of the number of mL of 0.1M *sodium thiosulfate VS* required in the Assay for iodine. Each mL of the remainder is equivalent to 16.60 mg of KI.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Aqueous Iodine Oral Solution should be kept in a well-closed container, the materials of which are resistant to iodine.

Aqueous Iodine Oral Solution contains in 1 mL 50 mg of Iodine and about 130 mg of total iodine, free and combined.

Aqueous Iodine Oral Solution is intended to be diluted before use.

When aqueous iodine solution is prescribed or demanded, Aqueous Iodine Oral Solution shall be dispensed or supplied.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aqueous Phenol Injection

General Notices

DEFINITION

Aqueous Phenol Injection is a sterile solution of Phenol in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phenol, C_6H_6O

95.0 to 105.0% w/v of the stated amount.

IDENTIFICATION

To 1 mL add 10 mL of *water* and 0.1 mL of *iron(III) chloride solution R1*. A violet colour is produced which disappears on addition of 5 mL of *propan-2-ol*.

TESTS

Acidity

pH, 3.3 to 6.5, Appendix V L.

ASSAY

Dilute a quantity containing 250 mg of Phenol with sufficient *water* to produce 250 mL, transfer 25 mL to a 500 mL glass-stoppered flask and add 50 mL of *0.05M bromine VS* and 5 mL of *hydrochloric acid*, stopper, swirl occasionally during 30 minutes and allow to stand for a further 15 minutes. Add 5 mL of a 20% w/v solution of *potassium iodide*, taking care to avoid loss of bromine, shake thoroughly and titrate with 0.1M *sodium thiosulfate VS* until only a faint yellow colour remains. Add 0.1 mL of *starch mucilage* and 10 mL of *chloroform* and complete the titration with vigorous shaking. Repeat the operation without the injection. The difference between the titrations represents the amount of bromine required. Each mL of *0.05M bromine VS* is equivalent to 1.569 mg of C_6H_6O. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage w/v of C_6H_6O.

STORAGE

Aqueous Phenol Injection should be protected from light.

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The strength is stated as the percentage w/v of Phenol.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Arachis Oil

General Notices

Peanut Oil

(Refined Arachis Oil, Ph. Eur. monograph 0263)

Preparation

Arachis Oil Enema

Ph Eur

DEFINITION

The refined fatty oil obtained from the shelled seeds of *Arachis hypogaea* L. A suitable antioxidant may be added.

CHARACTERS

Appearance

Clear, yellowish, viscous liquid.

Solubility

Very slightly soluble in ethanol (96 per cent), miscible with light petroleum.

Relative density

About 0.915.

It solidifies at about 2 °C.

IDENTIFICATION

First identification: B.

Second identification: A.

A. Identification of fatty oils by thin-layer chromatography (2.3.2).

Results The chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

B. Composition of fatty acids (see Tests).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acid value (2.5.1)

Maximum 0.5, determined on 10.0 g.

Peroxide value (2.5.5, Method A)

Maximum 5.0.

Unsaponifiable matter (2.5.7)

Maximum 1.0 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19)

It complies with the test.

Composition of fatty acids (2.4.22, Method A)

Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

— *saturated fatty acids of chain length less than* C_{16}: maximum 0.4 per cent;

— *palmitic acid*: 5.0 per cent to 14.0 per cent;

— *stearic acid*: 1.3 per cent to 6.5 per cent;

— *oleic acid*: 35.0 per cent to 76.0 per cent;

— *linoleic acid*: 8.0 per cent to 43.0 per cent;

— *linolenic acid*: maximum 0.6 per cent;

— *arachidic acid*: 0.5 per cent to 3.0 per cent;

— *eicosenoic acid*: 0.5 per cent to 3.0 per cent;

— *behenic acid*: 1.0 per cent to 5.0 per cent;

— *erucic acid*: maximum 0.5 per cent;

— *lignoceric acid*: 0.5 per cent to 3.0 per cent.

Water (2.5.32)

Maximum 0.1 per cent, determined on 1.00 g.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

In a well-filled container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Arachis Oil Enema

General Notices

DEFINITION

Arachis Oil Enema is Arachis Oil in a suitable container.

The enema complies with the requirements stated under Rectal Preparations and with the following requirements.

IDENTIFICATION

Carry out the test for *identification of fatty oils by thin-layer chromatography*, Appendix X N. The chromatogram obtained from the oil being examined shows spots corresponding to those in the *typical chromatogram* for arachis oil.

TESTS

Acid value

Not more than 0.6, Appendix X B.

Alkaline impurities

Complies with the test for *alkaline impurities*, Appendix X N.

Peroxide value

Not more than 5.0, Appendix X F.

Relative density

0.912 to 0.918, Appendix V G.

Unsaponifiable matter

Not more than 1.0% w/w, Appendix X H, Method II. Use 5 g.

Foreign fixed oils

Carry out the test for *composition of fatty acids by gas chromatography*, Appendix X N. The fatty-acid fraction of the oil has the following composition.

Saturated fatty acids of chain length less than C_{16} Not more than 0.4%.

Palmitic acid 7.0 to 16.0%.

www.webofpharma.com

https://thietbiuocngocanh.com/

Stearic acid 1.3 to 6.5%.

Oleic acid 35.0 to 72.0%.

Linoleic acid (equivalent chain length on polyethylene glycol adipate 18.9) 13.0 to 43.0%.

Linolenic acid (equivalent chain length on polyethylene glycol adipate 19.7) Not more than 0.6%.

Arachidic acid 1.0 to 3.0%.

Gadoleic acid (equivalent chain length on polyethylene glycol adipate 20.3) 0.5 to 2.1%.

Behenic acid 1.0 to 5.0%.

Erucic acid (equivalent chain length on polyethylene glycol adipate 22.3) Not more than 0.5%.

Lignoceric acid 0.5 to 3.0%.

The ratio of linoleic acid to behenic acid is not more than 15.

Semi-drying oils

To 1.0 g of the oil being examined add 5 mL of a mixture of 3 volumes of 2M *ethanolic potassium hydroxide* and 1 volume of *ethanol (96%)*, boil under a reflux condenser for 5 minutes, add 1.5 mL of 5M *acetic acid* and 50 mL of *ethanol (70%)* and heat until the solution is clear. Allow to cool or cool very slowly with a thermometer in the liquid. The temperature at which the liquid begins to become cloudy is not lower than 36°.

Sesame oil

Shake 10 mL with 5 mL of a mixture of 0.5 volume of a 0.35% v/v solution of *furfuraldehyde* in *acetic anhydride* and 4.5 volumes of *acetic anhydride* for 1 minute, filter the solution through a filter paper impregnated with *acetic anhydride* and add 0.2 mL of *sulfuric acid*. No bluish green colour develops.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

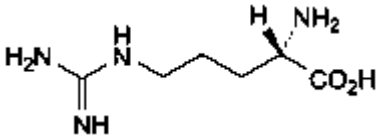
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Arginine

General Notices

(Ph. Eur. monograph 0806)



$C_6H_{14}N_4O_2$ 174.2 *74-79-3*

Action and use

Amino acid; nutrient.

Ph Eur

DEFINITION

(2*S*)-2-Amino-5-guanidinopentanoic acid.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, hygroscopic.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

www.webofpharma.com

https://thuocngocanh.com/

A. Specific optical rotation (see Tests).

B. Solution S (see Tests) is strongly alkaline (2.2.4).

C. Infrared absorption spectrophotometry (2.2.24).

Comparison arginine CRS.

If the spectra obtained show differences, dry the substance to be examined and the reference substance in an oven at 105 °C and record new spectra.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a 10.3 g/L solution of hydrochloric acid R and dilute to 50 mL with the same solution.

Reference solution Dissolve 10 mg of arginine CRS in a 10.3 g/L solution of hydrochloric acid R and dilute to 50 mL with the same solution.

Plate TLC silica gel plate R.

Mobile phase concentrated ammonia R, 2-propanol R (30:70 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 105 °C until the ammonia disappears completely.

Detection Spray with ninhydrin solution R and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

E. Dissolve about 25 mg in 2 mL of water R. Add 1 mL of α-naphthol solution R and 2 mL of a mixture of equal volumes of strong sodium hypochlorite solution R and water R. A red colour develops.

TESTS

Solution S

Dissolve 2.5 g in distilled water R and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

+ 25.5 to + 28.5 (dried substance).

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 2.00 g in *hydrochloric acid R1* and dilute to 25.0 mL with the same acid.

Ninhydrin-positive substances

Amino acid analysis (*2.2.56*). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter *2.2.46* are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A *water R* or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of *isoleucine R* and 30 mg of *leucine R* in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of arginine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.5 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (*2.4.4*)

Maximum 200 ppm.

To 5 mL of solution S add 0.5 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 300 ppm.

To 10 mL of solution S, add 1.7 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of *water R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 17.42 mg of $C_6H_{14}N_4O_2$.

www.webofpharma.com

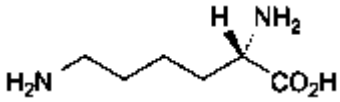
https://thuocngocanh.com/

STORAGE

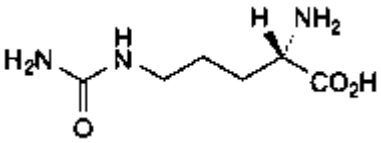
In an airtight container, protected from light.

IMPURITIES

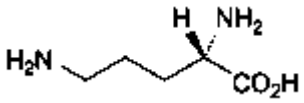
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



A. (2*S*)-2,6-diaminohexanoic acid (lysine),



B. (2*S*)-2-amino-5-(carbamoylamino)pentanoic acid (citrulline),



C. (2*S*)-2,5-diaminopentanoic acid (ornithine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

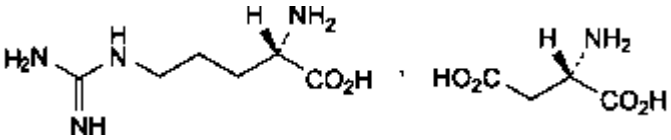
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Arginine Aspartate

General Notices

(Ph. Eur. monograph 2096)



$C_{10}H_{21}N_5O_6$ 307.3 *7675-83-4*

Action and use

Amino acid; nutrient.

Ph Eur

DEFINITION

(2*S*)-2-Amino-5-guanidinopentanoic acid (2*S*)-2-aminobutanedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white granules or powder.

Solubility

Very soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *arginine aspartate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

C. Examine the chromatograms obtained in the test for ninhydrin-positive substances.

Results The 2 principal spots in the chromatogram obtained with test solution (b) are similar in position, colour and size to the 2 principal spots in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

6.0 to 7.0 for solution S.

Specific optical rotation (*2.2.7*)

+ 25 to + 27 (dried substance).

Dissolve 2.50 g in *dilute hydrochloric acid R* and dilute to 25.0 mL with the same acid.

Ninhydrin-positive substances

Thin-layer chromatography (*2.2.27*).

Test solution (a) Dissolve 0.20 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *water R*.

Reference solution (a) Dissolve 25 mg of *arginine R* and 25 mg of *aspartic acid R* in *water R* and dilute to 25 mL with the same solvent.

Reference solution (b) Dilute 2 mL of reference solution (a) to 50 mL with *water R*.

Plate *TLC silica gel G plate R*.

Mobile phase *ammonia R*, *propanol R* (36:64 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 100-105 °C for 10 min.

Detection Spray with *ninhydrin solution R* and heat at 100-105 °C for 10 min.

System suitability Reference solution (b):

www.webofpharma.com

https://thuocngocanh.com/

— the chromatogram shows 2 clearly separated principal spots.

Limit Test solution (a):

— *any impurity*: any spots, apart from the 2 principal spots, are not more intense than each of the 2 principal spots in the chromatogram obtained with reference solution (b) (0.2 per cent).

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 300 ppm.

To 0.5 g add 2.5 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*. Examine after 30 min.

Ammonium (*2.4.1*)

Maximum 100 ppm, determined on 100 mg.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 60 °C for 24 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 80.0 mg in 2 mL of *anhydrous formic acid R*. Add 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 10.24 mg of $C_{10}H_{21}N_5O_6$.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

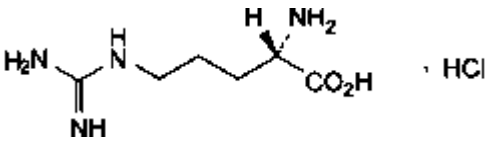
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Arginine Hydrochloride

General Notices

(Ph. Eur. monograph 0805)



$C_6H_{15}ClN_4O_2$ 210.7 *1119-34-2*

Action and use

Amino acid; nutrient.

Preparations

Arginine Hydrochloride Infusion

Arginine Hydrochloride Oral Solution

Arginine Hydrochloride Sterile Concentrate

Ph Eur

DEFINITION

(2*S*)-2-Amino-5-guanidinopentanoic acid hydrochloride.

Product of fermentation or of protein hydrolysis.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *arginine hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 50 mL with the same solvent.

Reference solution Dissolve 10 mg of *arginine hydrochloride CRS* in *water R* and dilute to 50 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *2-propanol R* (30:70 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 105 °C until the ammonia disappears completely.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 25 mg in 2 mL of *water R*. Add 1 mL of *α-naphthol solution R* and 2 mL of a mixture of equal volumes of *strong sodium hypochlorite solution R* and *water R*. A red colour develops.

E. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

www.webofpharma.com

https://thuocngocanh.com/

+ 21.0 to + 23.5 (dried substance).

Dissolve 2.00 g in *hydrochloric acid R1* and dilute to 25.0 mL with the same acid.

Ninhydrin-positive substances

Amino acid analysis (*2.2.56*). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter *2.2.46* are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A *water R* or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of *proline R* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of *ammonium standard solution (100 ppm NH_4) R* to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of *isoleucine R* and 30 mg of *leucine R* in solution A and dilute to 50 mL with solution A. Dilute 1 mL of the solution to 200 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of arginine hydrochloride in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.2 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

Ammonium

Amino acid analysis (*2.2.56*) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.180 g in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 21.07 mg of $C_6H_{15}ClN_4O_2$.

STORAGE

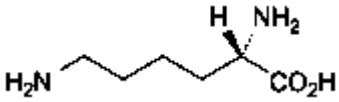
Protected from light.

www.webofpharma.com

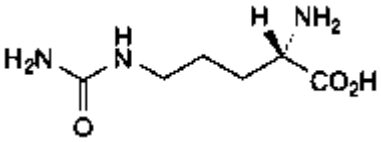
https://thuocngocanh.com/

IMPURITIES

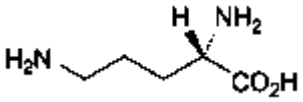
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



A. (2*S*)-2,6-diaminohexanoic acid (lysine),



B. (2*S*)-2-amino-5-(carbamoylamino)pentanoic acid (citrulline),



C. (2*S*)-2,5-diaminopentanoic acid (ornithine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Arginine Hydrochloride Infusion

General Notices

Arginine Hydrochloride Intravenous Infusion

Action and use

Amino acid; nutrient.

DEFINITION

Arginine Hydrochloride Infusion is a sterile solution containing Arginine Hydrochloride. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of arginine hydrochloride, $C_6H_{14}N_4O_2,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the test for Ninhydrin-positive substances the spot in the chromatogram obtained with solution (2) is similar in position, size and intensity to the spot in the chromatogram obtained with solution (4).

B. Dilute a suitable volume of the infusion with sufficient *water* to produce a solution containing 1.25% w/v of Arginine Hydrochloride. To 2 mL of the resulting solution add 1 mL of *1-naphthol solution* and 2 mL of a mixture of equal volumes of *sodium hypochlorite solution (3% Cl)* and *water*. A red colour develops.

C. Dilute a suitable volume of the infusion with sufficient *water* to produce a solution containing 0.5% w/v of Arginine Hydrochloride. The resulting solution yields reaction A characteristic of *chlorides*.

TESTS

Particulate contamination

When supplied in a container with a nominal volume of more than 100 mL, complies with the test for *sub-visible particles*, Appendix XIII A.

Acidity

pH, 5.0 to 6.5, Appendix V L.

Ninhydrin-positive substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Dilute the infusion to contain 1.0% w/v of Arginine Hydrochloride.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of solution (1) to 50 volumes.

(3) Dilute 1 volume of solution (2) to 4 volumes.

(4) 0.02% w/v of *arginine hydrochloride BPCRS*.

(5) 0.04% w/v each of *arginine hydrochloride BPCRS* and *lysine hydrochloride EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat it at 100° to 105° until the ammonia is removed. Spray with *ninhydrin solution* and heat at 100° to 105° for 15 minutes.

MOBILE PHASE

30 volumes of *concentrated ammonia* and 70 volumes of *propan-2-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (5) shows two clearly separated spots.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

Bacterial endotoxins

The endotoxin limit concentration is 0.5 IU per mL, Appendix XIV C. Dilute infusions containing more than 5.0% w/v of Arginine Hydrochloride with *water BET* to contain 5% w/v.

ASSAY

Dissolve 28 g of *potassium hydroxide* and 2 g of *potassium sodium (+)-tartrate* in 100 mL of *water*, add to the cooled solution 0.1 g of *2,4-dichloro-1-naphthol*, 180 mL of *ethanol (96%)* and 20 mL of a solution prepared by diluting 1 volume of *sodium hypochlorite solution (3% Cl)* to 6 volumes with *water* and allow the mixture to stand for 1 hour (solution A). Dilute a suitable volume of the infusion with sufficient *water* to produce a solution containing 0.004% w/v of Arginine Hydrochloride. To 5 mL add 5 mL of a 0.3% w/v solution of *potassium iodide*, mix and allow to stand for 15 minutes. Add 15 mL of solution A, mix and allow to stand for 15 minutes. Add 5 mL of a solution prepared by diluting 1 volume of *sodium hypochlorite solution (3% Cl)* to 15 volumes with *water* and allow to stand for 15 minutes. Measure the *absorbance* of the resulting solution at the maximum at 520 nm, Appendix II B, using *water* in the reference cell. Repeat the procedure using 5 mL of a 0.004% w/v solution of *arginine hydrochloride BPCRS* in *water* beginning at the words ‘add 5 mL of a 0.3% w/v solution of *potassium iodide* …’. Calculate the content of $C_6H_{14}N_4O_2$,HCl from the absorbances obtained using the declared content of $C_6H_{14}N_4O_2$,HCl in *arginine hydrochloride BPCRS*.

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The label states that solutions containing visible solid particles must not be used.

IMPURITIES

The impurities limited by the requirements of the monograph include ornithine.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Arginine Hydrochloride Oral Solution

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Amino acid; nutrient.

DEFINITION

Arginine Hydrochloride Oral Solution is a solution of Arginine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of arginine hydrochloride, $C_6H_{14}N_4O_2$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a suitable volume of the oral solution with sufficient *water* to produce a solution containing 1.25% w/v of Arginine Hydrochloride. To 2 mL of the resulting solution add 1 mL of *1-naphthol solution* and 2 mL of a mixture of equal volumes of *sodium hypochlorite solution (3% Cl)* and *water*. A red colour develops.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Ninhydrin-positive substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the oral solution with *water* to produce a solution containing 1% w/v of Arginine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 50 volumes with *water* and further dilute 1 volume of the resulting solution to 4 volumes with *water*.

(3) 0.04% w/v of each of *arginine hydrochloride BPCRS* and *lysine hydrochloride EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat at 100° to 105° until the ammonia is removed. Spray with *ninhydrin solution* and heat at 100° to 105° for 15 minutes.

MOBILE PHASE

50 volumes of *concentrated ammonia* and 50 volumes of *propan-2-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral solution containing 0.4 g of Arginine Hydrochloride to 100 mL with *water*.

(2) 0.4% w/v of *arginine hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

100 volumes of *methanol* and 400 volumes of 0.2M *sodium dihydrogen orthophosphate* containing 0.3% w/v of *sodium dodecyl sulfate*; adjust the pH to 3.3 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency* is at least 1800 *theoretical plates* per metre.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_6H_{14}N_4O_2$,HCl, weight in volume, using the declared content of $C_6H_{14}N_4O_2$,HCl in *arginine hydrochloride BPCRS*.

STORAGE

www.webofpharma.com

https://thietbiuocngocanh.com/

Arginine Hydrochloride Oral Solution should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Argon

General Notices

(Ph. Eur. monograph 2407)

Ar 39.95 *7440-37-1*

Ph Eur

DEFINITION

Gas obtained by fractional distillation of ambient air.

Content

Minimum 99.995 per cent *V/V* of Ar, calculated by deduction of the sum of impurities found when performing the test for impurities and the water content.

This monograph applies to argon for medicinal use.

CHARACTERS

Appearance

Colourless gas.

Solubility

At 20 °C and at a pressure of 101 kPa, 1 volume dissolves in about 29 volumes of water.

IDENTIFICATION

A. Verify that the gas is not oxygen using a paramagnetic analyser (*2.5.27*).

B. Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas (a) Ambient air.

Reference gas (b) *Argon R1*.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: molecular sieve for chromatography R (0.5 nm).

Carrier gas helium for chromatography R.

Flow rate 40 mL/min.

Temperature:

— *column*: 50 °C;

— *detector*: at a constant temperature between 50 °C and 200 °C.

Detection Thermal conductivity.

Injection 1 mL loop injector.

System suitability Reference gas (a):

— *resolution*: minimum 1.5 between the peaks due to argon/oxygen and nitrogen.

Results The principal peak in the chromatogram obtained with the gas to be examined is similar in retention time to the principal peak in the chromatogram obtained with reference gas (b).

TESTS

Impurities

Gas chromatography (2.2.28).

Gas to be examined The substance to be examined.

Reference gas Use the following mixture of gases in argon R1: methane R1 (5 ppm *V/V*), nitrogen R1 (5 ppm *V/V*), oxygen R (5 ppm *V/V*).

Column:

— *material*: stainless steel;

— *size*: *l* = 4 m, Ø = 4 mm;

— *stationary phase*: molecular sieve for chromatography R (0.5 nm).

Carrier gas argon R1.

Flow rate 70 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Temperature:

— *column*: 80 °C;

— *detector*: 40 °C.

Detection Discharge ionisation.

Injection 1 mL.

Sample rate 100 mL/min.

Relative retention With reference to impurity C (retention time = about 4.7 min): impurity A = about 0.4; impurity B = about 0.7.

System suitability Reference gas:

— *resolution*: minimum 3.0 between the peaks due to impurities A and B and minimum 2.0 between the peaks due to impurities B and C.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (5.0 ppm *V/V*);

— *total*: maximum 0.0040 per cent of the sum of the areas of all the peaks (40.0 ppm *V/V*).

Water (*2.5.28*)

Maximum 10.0 ppm *V/V*, determined using an electrolytic hygrometer.

STORAGE

In gaseous or liquid state, in suitable containers, complying with the legal regulations.

IMPURITIES

Specified impurities *A, D*.

Other detectable impurities *B, C*.

A. O_2: oxygen,

B. N_2: nitrogen,

C. CH_4: methane,

D. H_2O: water.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

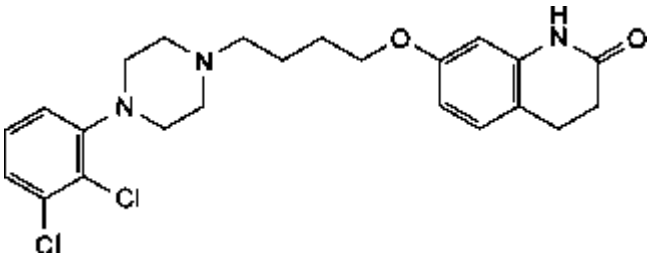
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aripiprazole

General Notices

(Ph. Eur. monograph 2617)



$C_{23}H_{27}Cl_2N_3O_2$ 448.4 *129722-12-9*

Action and use

Dopamine D_2 receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one.

Content

98.0 per cent to 102.0 per cent (dried substance).

PRODUCTION

It is considered that impurities 7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1*H*)-one, 7-(4-chlorobutoxy)-3,4-dihydroquinolin-2(1*H*)-one and 7-(4-iodobutoxy)-3,4-dihydroquinolin-2(1*H*)-one are genotoxic and are potential impurities in aripiprazole. These impurities are controlled by a suitable validated method.

CHARACTERS

Appearance

White or almost white crystals or crystalline powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, very slightly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison aripiprazole CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methylene chloride R, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

If intended for use in the manufacture of parenteral preparations, the solution is clear (2.2.1) and not more intensely coloured than reference solution GY_5 (2.2.2, Method II).

Dissolve 0.5 g in a mixture of 10 volumes of acetic acid R and 90 volumes of anhydrous ethanol R and dilute to 20 mL with the same mixture of solvents. Sonicate for about 15 min, shaking occasionally, until dissolution is complete.

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light.*

Solvent mixture acetic acid R, methanol R, acetonitrile R, water R (1:10:30:60 *V/V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of aripiprazole impurity F CRS in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 50 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of aripiprazole CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3 µm).

Mobile phase:

— *mobile phase A*: acetonitrile R, 0.05 per cent *V/V* solution of trifluoroacetic acid R (10:90 *V/V*);

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: 0.05 per cent *V/V* solution of *trifluoroacetic acid R*, *acetonitrile R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 10	80 → 65	20 → 35
10 - 20	65 → 10	35 → 90
20 - 25	10	90

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Relative retention With reference to aripiprazole (retention time = about 11 min): impurity F = about 1.1.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to aripiprazole and impurity F.

Calculation of percentage contents:

— for each impurity, use the concentration of aripiprazole in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Dissolve 1.0 mg of the substance to be examined in 20 mL of a 5.17 g/L solution of *hydrochloric acid R*.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (c).

System suitability Reference solution (c):

— *symmetry factor*: maximum 2.0.

Calculate the percentage content of $C_{23}H_{27}Cl_2N_3O_2$ taking into account the assigned content of *aripiprazole CRS*.

STORAGE

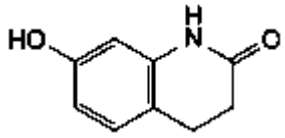
Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

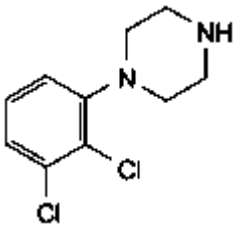
The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

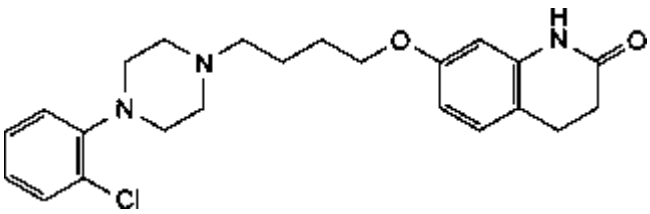
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G.*



A. 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one,



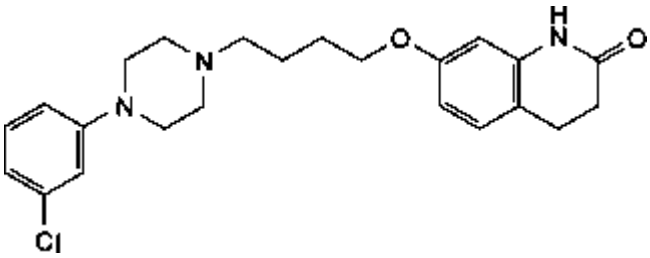
B. 1-(2,3-dichlorophenyl)piperazine,



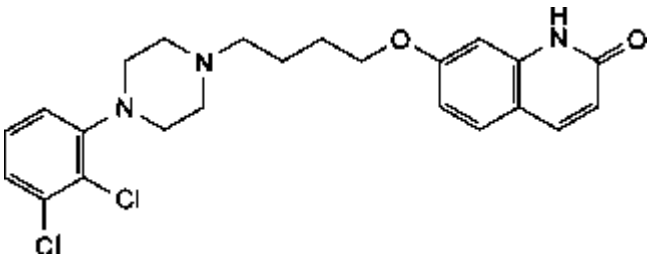
C. 7-[4-[4-(2-chlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one,

www.webofpharma.com

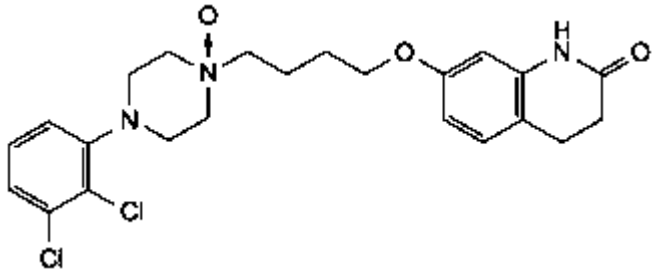
https://thuocngocanh.com/



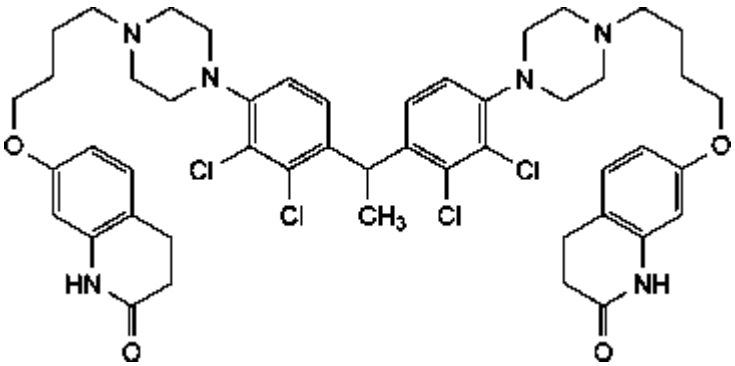
D. 7-[4-[4-(3-chlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one,



E. 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]quinolin-2(1*H*)-one,



F. 4-(2,3-dichlorophenyl)-1-[4-[(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy]butyl]piperazine 1-oxide,



G. 7,7′-[ethane-1,1-diylbis[(2,3-dichloro-4,1-phenylene)piperazine-4,1-diylbutane-4,1-diyloxy]]di(3,4-dihydroquinolin-2(1*H*)-one).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aromatic Ammonia Solution

General Notices

Sal Volatile Solution

DEFINITION

Ammonium Bicarbonate	25 g
Nutmeg Oil	0.3 mL
Lemon Oil	0.5 mL
Ethanol (90 per cent)	37.5 mL
Strong Ammonia Solution	67.5 mL
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

Extemporaneous preparation

The following directions apply.

Dissolve the Ammonium Bicarbonate in 800 mL of the Purified Water. Separately dissolve the Lemon Oil and the Nutmeg Oil in the Ethanol (90 per cent). Add the ethanolic solution to the aqueous solution and add the Strong Ammonia Solution and sufficient Purified Water to produce 1000 mL. Add 25 g of previously sterilised Purified Talc, shake, allow to stand for a few hours, shaking occasionally, and filter.

Content of free ammonia, NH_3

1.12 to 1.25% w/v.

Content of ammonium carbonate, $(NH_4)_2CO_3$

2.76 to 3.24% w/v.

TESTS

Ethanol content

2.6 to 3.5% v/v when determined by the following method.

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions:

(1) 1.5% v/v of *absolute ethanol* and 1.5% v/v of *propan-1-ol* (internal standard).

(2) Dilute a volume of the preparation being examined with *water* to contain between 1.0% and 2.0% v/v of ethanol.

www.webofpharma.com

https://thuocngocanh.com/

(3) Prepare solution in the same manner as solution (2) but adding sufficient of the internal standard to produce a final concentration of 1.5% v/v.

CHROMATOGRAPHIC CONDITIONS

(a) Use a column (1.5 m × 4 mm) packed with porous polymer beads (100 to 120 mesh) (Porapak Q and Chromosorb 101 are suitable).

(b) Use *helium* as the carrier gas at 1.7 mL per minute.

(c) Use isothermal conditions maintained at 150°.

(d) Use an inlet temperature of 170°.

(e) Use a flame ionisation detector at a temperature of 170°.

(f) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the percentage content of ethanol in the solution from the areas of the peaks due to ethanol in the chromatograms obtained with solutions (1) and (3).

Weight per mL

0.980 to 1.005 g, Appendix V G.

ASSAY

For free ammonia

To 20 mL add 50 mL of *1M hydrochloric acid VS*, boil, cool and titrate the excess of acid with *1M sodium hydroxide VS* using *methyl red solution* as indicator. Each mL of *1M hydrochloric acid VS*, after subtraction of the volume of *1M sodium hydroxide VS* required in the Assay for ammonium carbonate, is equivalent to 17.03 mg of NH_3.

For ammonium carbonate

To 20 mL add 25 mL of *1M sodium hydroxide VS* and 40 mL of *barium chloride solution*, heat on a water bath for 15 minutes, cool, add 10 mL of *formaldehyde solution* previously neutralised to *thymol blue solution* and titrate the excess of alkali with *1M hydrochloric acid VS*, using *thymol blue solution* as indicator, to the grey colour indicative of pH 8.8. Each mL of *1M sodium hydroxide VS* is equivalent to 48.04 mg of $(NH_4)_2CO_3$.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aromatic Ammonia Spirit

General Notices

Sal Volatile Spirit

DEFINITION

Nutmeg Oil	3 mL
Lemon Oil	5 mL
Ethanol (90 per cent)	750 mL
Ammonium Bicarbonate	25 g
Strong Ammonia Solution	67.5 mL
Purified Water	Sufficient to produce 1000 mL

Extemporaneous preparation

The following directions apply.

Distil a mixture of the Lemon Oil, the Nutmeg Oil, the Ethanol (90 per cent) and 375 mL of Purified Water. Reserve the first 875 mL of distillate. Distil a further 55 mL and add the Ammonium Bicarbonate and the Strong Ammonia Solution to the distillate. Heat on a water bath to 60° in a sealed bottle of not less than 120 mL capacity, shaking occasionally, until solution is complete, cool, filter through absorbent cotton, mix the filtrate with the reserved distillate, add sufficient Purified Water to produce 1000 mL and mix.

The spirit complies with the requirements stated under Spirits and with the following requirements.

Content of free ammonia, NH_3

1.12 to 1.30% w/v.

Content of ammonium carbonate, $(NH_4)_2CO_3$

2.76 to 3.24% w/v.

TESTS

Ethanol content

64 to 70% v/v, Appendix VIII F.

Weight per mL

www.webofpharma.com

https://thuocngocanh.com/

0.880 to 0.893 g, Appendix V G.

ASSAY

For free ammonia

To 20 mL add 50 mL of *1M hydrochloric acid VS*, boil, cool and titrate the excess of acid with *1M sodium hydroxide VS* using *methyl red solution* as indicator. Each mL of *1M hydrochloric acid VS*, after subtraction of the volume of *1M sodium hydroxide VS* required in the Assay for ammonium carbonate, is equivalent to 17.03 mg of NH_3.

For ammonium carbonate

To 20 mL add 25 mL of *1M sodium hydroxide VS* and 40 mL of *barium chloride solution*, heat on a water bath for 15 minutes, cool, add 10 mL of *formaldehyde solution* previously neutralised to *thymol blue solution* and titrate the excess of alkali with *1M hydrochloric acid VS*, using *thymol blue solution* as indicator, to the grey colour indicative of pH 8.8. Each mL of *1M sodium hydroxide VS* is equivalent to 48.04 mg of $(NH_4)_2CO_3$.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aromatic Magnesium Carbonate Mixture

General Notices

Aromatic Magnesium Carbonate Oral Suspension

DEFINITION

Aromatic Magnesium Carbonate Mixture is an *oral suspension* containing 3% w/v of Light Magnesium Carbonate and 5% w/v of Sodium Bicarbonate in a suitable vehicle containing Aromatic Cardamom Tincture.

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of sodium bicarbonate, $NaHCO_3$

4.7 to 5.3% w/v.

Content of magnesium, Mg

0.70 to 0.86% w/v.

ASSAY

For sodium bicarbonate

Boil 10 g with 100 mL of *water* for 5 minutes, filter, boil the residue with 100 mL of *water* for 5 minutes and filter. Combine the filtrates, cool and titrate with *0.5M hydrochloric acid VS* using *methyl orange–xylene cyanol FF solution* as indicator. Add 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. After subtracting one-fifth of the volume of 0.05M *disodium edetate VS*, each mL of *0.5M hydrochloric acid VS* is equivalent to 42.00 mg of $NaHCO_3$. Determine the *weight per mL* of the mixture, Appendix V G, and calculate the percentage of $NaHCO_3$, weight in volume.

For magnesium

Dissolve 30 g in the minimum quantity of *2M hydrochloric acid* and dilute to 200 mL with *water*. To 20 mL of this solution add 200 mL of *water* and 10 mL of *ammonia buffer pH 10.9* and titrate with 0.05M *disodium edetate VS* using *mordant black 11 solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 1.215 mg of Mg. Use the *weight per mL* of the mixture to calculate the percentage of Mg, weight in volume.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

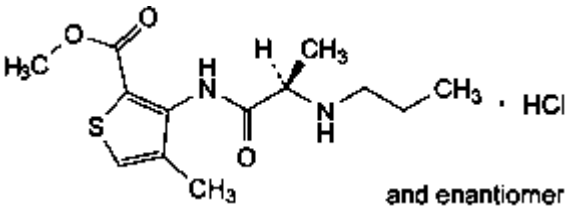
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Articaine Hydrochloride

General Notices

(Ph. Eur. monograph 1688)



$C_{13}H_{21}ClN_2O_3S$ 320.8 *23964-57-0*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

Methyl 4-methyl-3-[[(2*RS*)-2-(propylamino)propanoyl]amino]thiophene-2-carboxylate hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Dissolve 50.0 mg in a 1 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 5.0 mL of the solution to 100.0 mL with a 1 g/L solution of *hydrochloric acid R*. Examined between 200 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 272 nm. The specific absorbance at the maximum is 290 to 320.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Place dropwise 20 µL of the test solution on 300 mg discs.

Test solution Dissolve 0.1 g in 5 mL of *water R*, add 3 mL of a saturated solution of *sodium hydrogen carbonate R* and shake twice with 2 mL of *methylene chloride R*. Combine the methylene chloride layers, dilute to 5.0 mL with *methylene chloride R* and dry over *anhydrous sodium sulfate R*.

Comparison *articaine hydrochloride CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 20 mg of the substance to be examined in 5 mL of *ethanol (96 per cent) R*.

Reference solution Dissolve 20 mg of *articaine hydrochloride CRS* in 5 mL of *ethanol (96 per cent) R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *triethylamine R*, *ethyl acetate R*, *heptane R* (10:35:65 *V/V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 0.50 g in *water R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method I*).

pH (*2.2.3*)

www.webofpharma.com

https://thuocngocanh.com/

4.2 to 5.2.

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *articaine impurity A CRS* and 2.5 mg of *articaine impurity E CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase Mix 25 volumes of *acetonitrile R* and 75 volumes of a solution prepared as follows: dissolve 2.02 g of *sodium heptanesulfonate R* and 4.08 g of *potassium dihydrogen phosphate R* in *water R* and dilute to 1000 mL with the same solvent. Adjust to pH 2.0 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 276 nm.

Injection 10 µL.

Run time 5 times the retention time of articaine.

Relative retention With reference to articaine (retention time = about 9 min): impurity A = about 0.8; impurity E = about 0.86.

System suitability Reference solution (b):

— *resolution*: minimum 1.2 between the peaks due to impurities A and E.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *sum of impurities other than A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 5 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20) using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.08 mg of $C_{13}H_{21}ClN_2O_3S$.

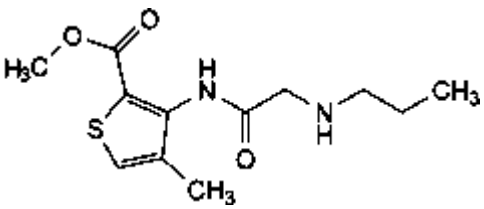
STORAGE

Protected from light.

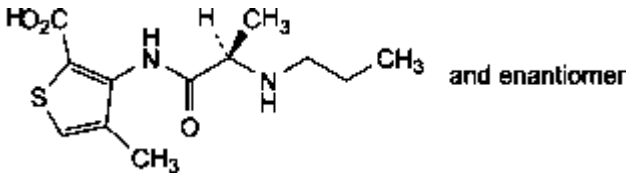
IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, F, G, H, I, J.



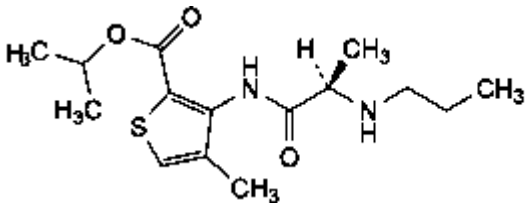
A. methyl 4-methyl-3-[[2-(propylamino)acetyl]amino]thiophene-2-carboxylate (acetamidoarticaine),



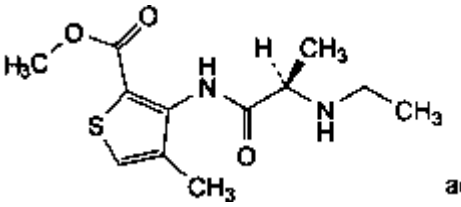
B. 4-methyl-3-[[(2*RS*)-2-(propylamino)propanoyl]amino]thiophene-2-carboxylic acid (articaine acid),

www.webofpharma.com

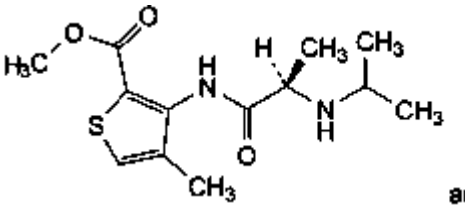
https://thuocngocanh.com/


and enantiomer

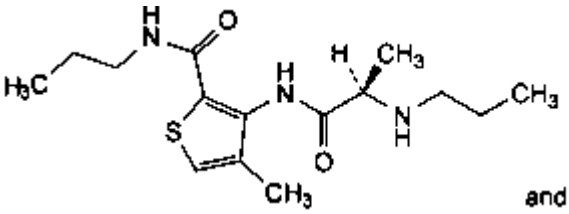
C. 1-methylethyl 4-methyl-3-[[(2*RS*)-2-(propylamino)propanoyl]amino]thiophene-2-carboxylate (articaine isopropyl ester),


and enantiomer

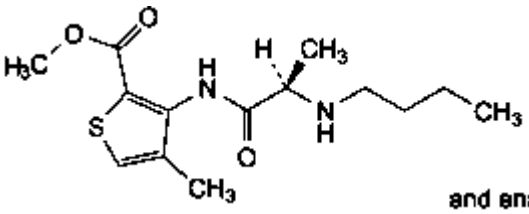
D. methyl 3-[[(2*RS*)-2-(ethylamino)propanoyl]amino]-4-methylthiophene-2-carboxylate (ethylarticaine),


and enantiomer

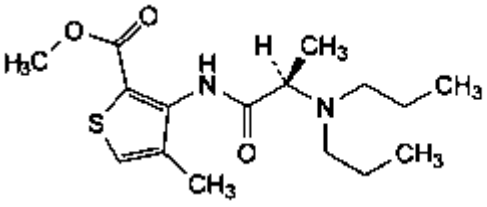
E. methyl 4-methyl-3-[[(2*RS*)-2-[(1-methylethyl)amino]propanoyl]amino]thiophene-2-carboxylate (isopropylarticaine),


and enantiomer

F. 4-methyl-*N*-propyl-3-[[(2*RS*)-2-(propylamino)propanoyl]amino]thiophene-2-carboxamide (articaine acid propionamide),


and enantiomer

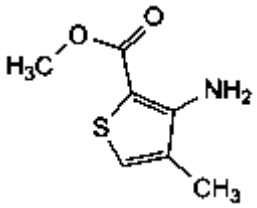
G. methyl 3-[[(2*RS*)-2-(butylamino)propanoyl]amino]-4-methylthiophene-2-carboxylate (butylarticaine),


and enantiomer

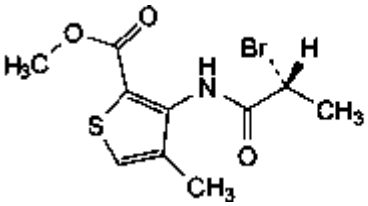
H. methyl 3-[[(2*RS*)-2-(dipropylamino)propanoyl]amino]-4-methylthiophene-2-carboxylate (dipropylarticaine),

www.webofpharma.com

https://thuocngocanh.com/



I. methyl 3-amino-4-methylthiophene-2-carboxylate (3-aminoarticaine),



and enantiomer

J. methyl 3-[[(2*RS*)-2-bromopropanoyl]amino]-4-methylthiophene-2-carboxylate (bromo compound).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

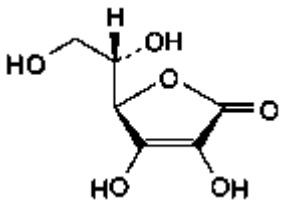
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Ascorbic Acid

General Notices

(Ph. Eur. monograph 0253)



$C_6H_8O_6$ 176.1 *50-81-7*

Action and use

Vitamin C.

Preparations

Ascorbic Acid Injection

Ascorbic Acid Tablets

Ascorbic Acid Chewable Tablets

Paediatric Vitamins A, C and D Oral Drops

Potassium Ascorbate Eye Drops

Vitamins B and C Injection

When Vitamin C is prescribed or demanded, Ascorbic Acid shall be dispensed or supplied.

Ph Eur

DEFINITION

(5*R*)-5-[(1*S*)-1,2-Dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one.

Content

99.0 per cent to 100.5 per cent.

www.webofpharma.com

https://thuocngocanh.com/

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, becoming discoloured on exposure to air and moisture.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent).

mp

About 190 °C, with decomposition.

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.10 g in *water R* and dilute immediately to 100.0 mL with the same solvent. Add 1.0 mL of the solution to 10 mL of a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with *water R*.

Absorption maximum 243 nm, determined immediately after dissolution.

Specific absorbance at the absorption maximum 545 to 585.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *ascorbic acid CRS*.

C. pH (2.2.3): 2.1 to 2.6 for solution S (see Tests).

D. To 1 mL of solution S add 0.2 mL of *dilute nitric acid R* and 0.2 mL of *silver nitrate solution R2*. A grey precipitate is formed.

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

www.webofpharma.com

https://thuvienthuocngocanh.com/

+ 20.5 to + 21.5.

Dissolve 2.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Impurity E

Maximum 0.2 per cent.

Test solution Dissolve 0.25 g in 5 mL of *water R*. Neutralise using *dilute sodium hydroxide solution R*, then add 1 mL of *dilute acetic acid R* and 0.5 mL of *calcium chloride solution R*.

Reference solution Dissolve 70 mg of *oxalic acid R* (dihydrate of impurity E) in *water R* and dilute to 500 mL with the same solvent; to 5 mL of the solution add 1 mL of *dilute acetic acid R* and 0.5 mL of *calcium chloride solution R*.

Allow the solutions to stand for 1 h. Any opalescence in the test solution is not more intense than that in the reference solution.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Phosphate buffer solution Dissolve 6.8 g of *potassium dihydrogen phosphate R* in *water for chromatography R* and dilute to about 200 mL with the same solvent. Filter through a membrane filter (nominal pore size 0.45 µm) and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 0.500 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 10.0 mg of *ascorbic acid impurity C CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *ascorbic acid impurity D CRS* and 5.0 mg of *ascorbic acid CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1 mL of the test solution to 200 mL with the mobile phase. Mix 1 mL of this solution and 1 mL of reference solution (a).

Reference solution (d) Dilute 2.5 mL of reference solution (a) to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase Phosphate buffer solution, *acetonitrile R1* (25:75 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 2.5 times the retention time of ascorbic acid.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to ascorbic acid (retention time = about 9 min): impurity D = about 0.5; impurity C = about 1.45.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to ascorbic acid and impurity C in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 20 for the peak due to impurity C in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— for impurity C, use the concentration of impurity C in reference solution (d);

— for impurity D, use the concentration of impurity D in reference solution (b);

— for impurities other than C and D, use the concentration of ascorbic acid in reference solution (b).

Limits:

— *impurities C, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than C and D*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Copper

Maximum 5 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 2.0 g in *0.1 M nitric acid* and dilute to 25.0 mL with the same acid.

Reference solutions Prepare the reference solutions (0.2 ppm, 0.4 ppm and 0.6 ppm) using *copper standard solution (10 ppm Cu) R*, diluting with *0.1 M nitric acid*.

Source Copper hollow-cathode lamp.

Wavelength 324.8 nm.

Atomisation device Air-acetylene flame.

www.webofpharma.com

https://thuocngocanh.com/

Adjust the zero of the apparatus using *0.1 M nitric acid*.

Iron

Maximum 2 ppm.

Atomic absorption spectrometry (*2.2.23*).

Test solution Dissolve 5.0 g in *0.1 M nitric acid* and dilute to 25.0 mL with the same acid.

Reference solutions Prepare the reference solutions (0.2 ppm, 0.4 ppm and 0.6 ppm) using *iron standard solution (20 ppm Fe) R*, diluting with *0.1 M nitric acid*.

Source Iron hollow-cathode lamp.

Wavelength 248.3 nm.

Atomisation device Air-acetylene flame.

Adjust the zero of the apparatus using *0.1 M nitric acid*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in a mixture of 10 mL of *dilute sulfuric acid R* and 80 mL of *carbon dioxide-free water R*. Add 1 mL of *starch solution R*. Titrate with *0.05 M iodine* until a persistent violet-blue colour is obtained.

1 mL of *0.05 M iodine* is equivalent to 8.81 mg of $C_6H_8O_6$.

STORAGE

In a non-metallic container, protected from light.

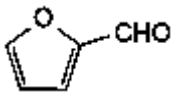
IMPURITIES

Specified impurities *C, D, E*.

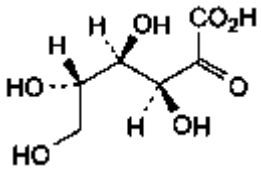
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, F, G, H*.

www.webofpharma.com

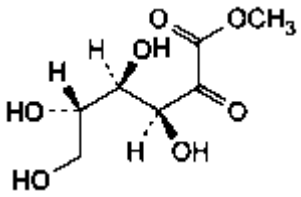
https://thuocngocanh.com/



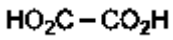
A. furan-2-carbaldehyde (furfural),



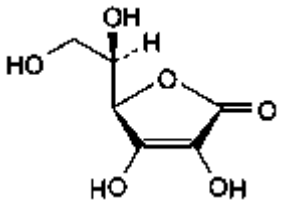
C. L-*xylo*-hex-2-ulosonic acid (L-sorbosonic acid),



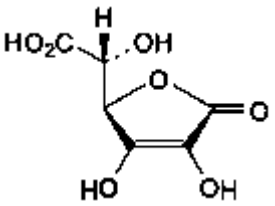
D. methyl L-*xylo*-hex-2-ulosonate (methyl L-sorbosonate),



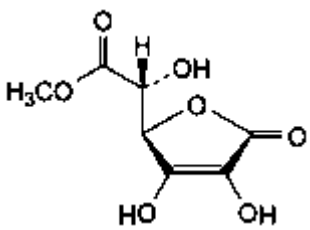
E. oxalic acid,



F. (5*R*)-5-[(1*R*)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one,



G. (*R*)-[(2*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]hydroxyacetic acid,



www.webofpharma.com

https://thuvienthuocngocanh.com/

H. methyl (*R*)-[(2*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]hydroxyacetate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ascorbic Acid Chewable Tablets

General Notices

Chewable Ascorbic Acid Tablets

Action and use

Vitamin C.

DEFINITION

Ascorbic Acid Chewable Tablets contain Ascorbic Acid.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ascorbic acid, $C_6H_8O_6$

95.0 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Ascorbic Acid with 10 mL of *water* for 15 minutes and filter.

(2) 0.5% w/v of *ascorbic acid BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

A mixture of 20 volumes of *water* and 120 volumes of *ethanol (96%)*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. Shake a quantity of the powdered tablets with *water* and filter. The filtrate is acidic to *litmus solution*, decolourises *2,6-dichlorophenolindophenol solution* and reduces *silver nitrate solution* immediately at room temperature producing a black precipitate.

www.webofpharma.com

https://thuathuocngocanh.com/

TESTS

Disintegration

The requirement for Disintegration does not apply to Ascorbic Acid Chewable Tablets.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.15 g of Ascorbic Acid as completely as possible in a mixture of 30 mL of *water* and 20 mL of 1M *sulfuric acid* and titrate with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 8.806 mg of $C_6H_8O_6$.

STORAGE

Ascorbic Acid Chewable Tablets should be kept free from contact with metal and protected from light and moisture.

When vitamin C chewable tablets are prescribed or demanded, Ascorbic Acid Chewable Tablets shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ascorbic Acid Injection

General Notices

Action and use

Vitamin C.

DEFINITION

Ascorbic Acid Injection is a sterile solution of Ascorbic Acid in Water for Injections containing Sodium Bicarbonate.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of ascorbic acid, $C_6H_8O_6$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless liquid.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Dilute the injection, if necessary, to contain 0.5% w/v of Ascorbic Acid.

(2) 0.5% w/v of *ascorbic acid BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *water* and 120 volumes of *ethanol (96%)*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thietbiuocngocanh.com/

B. To a volume containing 50 mg of Ascorbic Acid add 0.2 mL of 2M *nitric acid* and 0.2 mL of 0.1M *silver nitrate*. A grey precipitate is produced.

TESTS

Acidity

pH, 5.0 to 6.5, Appendix V L.

Oxalic acid

Dilute a volume containing 0.25 g to 5 mL with *water*, neutralise to *litmus paper* with 2M *sodium hydroxide*, add 1 mL of 2M *acetic acid* and 0.5 mL of *calcium chloride solution* and allow to stand for 1 hour. Any opalescence produced is not more intense than that in a solution prepared at the same time and in the following manner. Dissolve 70 mg of *oxalic acid* in 500 mL of *water* and to 5 mL of the resulting solution add 1 mL of 2M *acetic acid* and 0.5 mL of *calcium chloride solution* (0.3%).

ASSAY

To a volume containing 0.2 g add 5 mL of 2M *sulfuric acid* and titrate with *0.05M iodine VS* using *starch mucilage* as indicator. Each mL of *0.05M iodine VS* is equivalent to 8.806 mg of $C_6H_8O_6$.

STORAGE

Ascorbic Acid Injection should be protected from light and stored at a temperature of 2° to 8°.

When vitamin C injection is prescribed or demanded, Ascorbic Acid Injection shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ascorbic Acid Tablets

General Notices

Action and use

Vitamin C.

DEFINITION

Ascorbic Acid Tablets contain Ascorbic Acid.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ascorbic acid, $C_6H_8O_6$

95.0 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Ascorbic Acid with 10 mL of *water* for 15 minutes and filter.

(2) 0.5% w/v of *ascorbic acid BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *water* and 120 volumes of *ethanol (96%)*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. Shake a quantity of the powdered tablets with *water* and filter. The filtrate is acidic to *litmus solution*, decolourises *2,6-dichlorophenolindophenol solution* and reduces *silver nitrate solution* immediately at room temperature producing a black precipitate.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.15 g of Ascorbic Acid as completely as possible in a mixture of 30 mL of *water* and 20 mL of 1M *sulfuric acid* and titrate with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 8.806 mg of $C_6H_8O_6$.

STORAGE

Ascorbic Acid Tablets should be kept free from contact with metal and protected from light and moisture.

When vitamin C tablets are prescribed or demanded, Ascorbic Acid Tablets shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

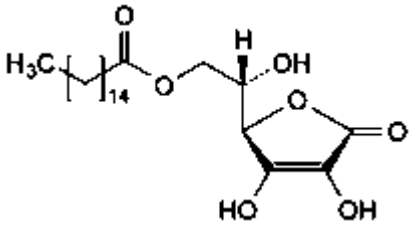
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ascorbyl Palmitate

General Notices

(Ph. Eur. monograph 0807)



$C_{22}H_{38}O_7$ 414.5 *137-66-6*

Action and use

Excipient.

Ph Eur

DEFINITION

(2*S*)-2-[(2*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]-2-hydroxyethyl hexadecanoate.

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent) and in methanol, practically insoluble in methylene chloride and in fatty oils.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *ascorbyl palmitate CRS*.

C. Dissolve about 10 mg in 5 mL of *methanol R*. The solution decolourises *dichlorophenolindophenol standard solution R*.

TESTS

Solution S

Dissolve 2.50 g in *methanol R* using sonication and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_4 (*2.2.2, Method I*).

Specific optical rotation (*2.2.7*)

+ 21 to + 24 (dried substance), determined on solution S.

Related substances

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 5 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *ethanol (96 per cent) R*. Add 30 mL of *water R* and titrate with *0.05 M iodine* until a yellow colour is obtained.

1 mL of *0.05 M iodine* is equivalent to 20.73 mg of $C_{22}H_{38}O_7$.

STORAGE

In an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

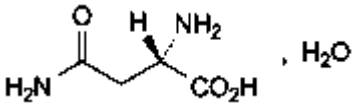
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Asparagine Monohydrate

General Notices

(Ph. Eur. monograph 2086)



$C_4H_8N_2O_3,H_2O$ 150.1 *5794-13-8*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2,4-Diamino-4-oxobutanoic acid monohydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A, B, D.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *asparagine monohydrate CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *asparagine monohydrate CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (25:25:50 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 110 °C for 15 min.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Loss on drying (see Tests).

TESTS

Solution S

Dissolve with heating 2.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.0 to 6.0 for solution S.

Specific optical rotation (*2.2.7*)

+ 33.7 to + 36.0 (dried substance).

Dissolve 2.50 g in a 309.0 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same acid.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *water R*.

Reference solution (c) Dissolve 5.0 mg of *aspartic acid R* (impurity A) in *water R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Reference solution (d) Dissolve 3.0 mg of *asparagine impurity C CRS* in 40 mL of the mobile phase using sonication and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Reference solution (e) Mix 5 mL of reference solution (c) with 2.5 mL of reference solution (a) and dilute to 10 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase Dissolve 13.6 g of *potassium dihydrogen phosphate R* and 2.16 g of *sodium octanesulfonate R* in about 900 mL of *water for chromatography R*. Adjust to pH 2.2 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*. Add 5 mL of *acetonitrile R1*.

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Run time Twice the retention time of asparagine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to asparagine (retention time = about 6.6 min): impurity C = about 0.6; impurity A = about 1.2.

System suitability Reference solution (e):

— *resolution*: minimum 5.0 between the peaks due to asparagine and impurity A.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (c);

— for impurity C, use the concentration of impurity C in reference solution (d);

— for impurities other than A and C, use the concentration of asparagine monohydrate in reference solution (b).

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity A*: maximum 0.5 per cent;

— *impurity C*: maximum 0.1 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.8 per cent;

— *reporting threshold*: 0.03 per cent.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 12.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

To 0.75 g add 2.5 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*. Examine after 30 min.

Ammonium (*2.4.1, Method B*)

Maximum 0.1 per cent, determined on 10 mg.

Prepare the standard using 0.1 mL of *ammonium standard solution (100 ppm NH_4) R*.

Iron (*2.4.9*)

Maximum 10 ppm.

Dissolve 1.0 g in *dilute hydrochloric acid R* and dilute to 10 mL with the same acid. Shake 3 times with 10 mL of *methyl isobutyl ketone R1* for 3 min. Wash the combined organic phases with 10 mL of *water R* for 3 min. The aqueous phase complies with the limit test for iron.

Loss on drying (*2.2.32*)

10.5 per cent to 12.5 per cent, determined on 1.000 g by drying in an oven at 130 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.110 g in 5 mL of *anhydrous formic acid R*. Add 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 13.21 mg of $C_4H_8N_2O_3$.

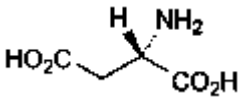
www.webofpharma.com

https://thuocngocanh.com/

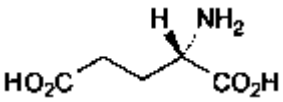
IMPURITIES

Specified impurities A, C.

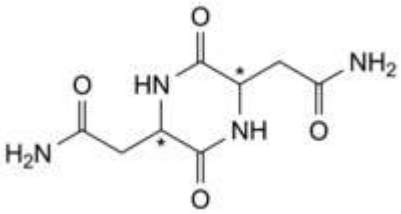
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, D, E, F, G, H.



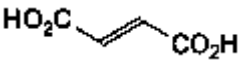
A. (2*S*)-2-aminobutanedioic acid (aspartic acid),



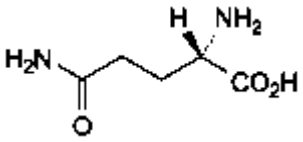
B. (2*S*)-2-aminopentanedioic acid (glutamic acid),



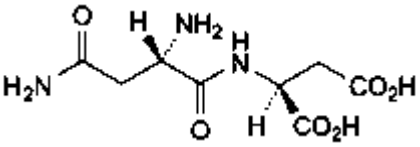
C. 2,2′-[(2Ξ,5Ξ)-3,6-dioxopiperazine-2,5-diyl]diacetamide,



D. (2*E*)-but-2-enedioic acid (fumaric acid),



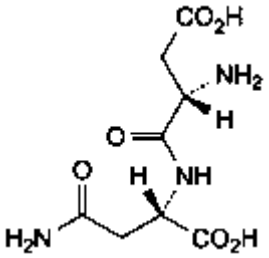
E. (2*S*)-2,5-diamino-5-oxopentanoic acid (glutamine),



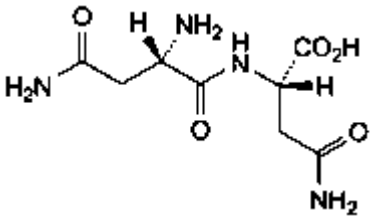
F. (2*S*)-2-[[(2*S*)-2,4-diamino-4-oxobutanoyl]amino]butanedioic acid (asparaginylaspartic acid),

www.webofpharma.com

https://thuocngocanh.com/



G. (2*S*)-4-amino-2-[[(2*S*)-2-amino-3-carboxypropanoyl]amino]-4-oxobutanoic acid (α-aspartylasparagine),



H. (2*S*)-4-amino-2-[[(2*S*)-2,4-diamino-4-oxobutanoyl]amino]-4-oxobutanoic acid (asparaginylasparagine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

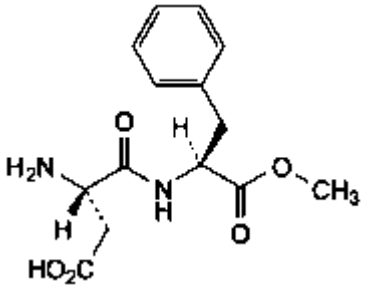
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspartame

General Notices

(Ph. Eur. monograph 0973)



$C_{14}H_{18}N_2O_5$ 294.3 *22839-47-0*

Action and use

Sweetening agent.

Ph Eur

DEFINITION

(3*S*)-3-Amino-4-[[(2*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino]-4-oxobutanoic acid (methyl α-L-aspartyl-L-phenylalaninate).

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Sparingly soluble or slightly soluble in water and in ethanol (96 per cent), practically insoluble in hexane and in methylene chloride.

IDENTIFICATION

First identification: B.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.1 g in *ethanol (96 per cent) R* and dilute to 100 mL with the same solvent.

Spectral range 230-300 nm.

Absorption maxima At 247 nm, 252 nm, 258 nm and 264 nm.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *aspartame CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 15 mg of the substance to be examined in 2.5 mL of *water R* and dilute to 10 mL with *acetic acid R*.

Reference solution Dissolve 15 mg of *aspartame CRS* in 2.5 mL of *water R* and dilute to 10 mL with *acetic acid R*.

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *anhydrous formic acid R*, *methanol R*, *methylene chloride R* (2:4:30:64 *V/V/V/V*).

Application 20 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 100-105 °C for 15 min.

Results The spot in the chromatogram obtained with the test solution is similar in position, colour and size to the spot in the chromatogram obtained with the reference solution.

D. Dissolve about 20 mg in 5 mL of *methanol R* and add 1 mL of *alkaline hydroxylamine solution R1*. Heat on a water-bath for 15 min. Allow to cool and adjust to about pH 2 with *dilute hydrochloric acid R*. Add 0.1 mL of *ferric chloride solution R1*. A brownish-red colour is produced.

TESTS

Solution S

Dissolve 0.8 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

Solution S is clear (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, Method II).

Conductivity (2.2.38)

Maximum 30 µS·cm^{-1}.

Dissolve 0.80 g in carbon dioxide-free water R prepared from distilled water R and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution (C_1) and that of the water used for preparing the solution (C_2). The readings must be stable within 1 per cent over a period of 30 s.

Calculate the conductivity of the solution of the substance to be examined using the following expression:

$$C_1 - 0.992\ C_2$$

Specific optical rotation (2.2.7)

+ 14.5 to + 16.5 (dried substance).

Dissolve 2.00 g in a 690 g/L solution of *anhydrous formic acid R* and dilute to 50.0 mL with the same solution. Measure within 30 min of preparation.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.60 g of the substance to be examined in a mixture of 1.5 volumes of glacial acetic acid R and 98.5 volumes of water R and dilute to 100.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 4.5 mg of aspartame impurity A CRS in a mixture of 1.5 volumes of glacial acetic acid R and 98.5 volumes of water R and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (b) Dissolve 30.0 mg of phenylalanine R (impurity C) in a mixture of 15 volumes of glacial acetic acid R and 85 volumes of water R and dilute to 100.0 mL with the same mixture of solvents. Dilute 1.0 mL of this solution to 10.0 mL with water R.

Reference solution (c) Dilute 5.0 mL of the test solution to 10.0 mL with water R. Dilute 3.0 mL of this solution to 100.0 mL with water R.

Reference solution (d) Dissolve 30.0 mg of L-aspartyl-L-phenylalanine R (impurity B) in a mixture of 15 volumes of glacial acetic acid R and 85 volumes of water R and dilute to 100.0 mL with the same mixture of solvents. Dilute 1.0 mL of the solution to 10.0 mL with water R. Mix 1.0 mL of this solution with 1.0 mL of reference solution (b).

Column

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5-10 µm).

Mobile phase Mix 10 volumes of acetonitrile R and 90 volumes of a 6.8 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 3.7 with phosphoric acid R.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time Twice the retention time of aspartame.

System suitability Reference solution (d):

— *resolution*: minimum 3.5 between the peaks due to impurities B and C.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *sum of impurities other than A and C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.5 per cent);

— *disregard limit*: disregard any peak due to the solvent.

Loss on drying (2.2.32)

Maximum 4.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 1.5 mL of *anhydrous formic acid R* and 60 mL of *anhydrous acetic acid R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 29.43 mg of $C_{14}H_{18}N_2O_5$.

STORAGE

In an airtight container.

IMPURITIES

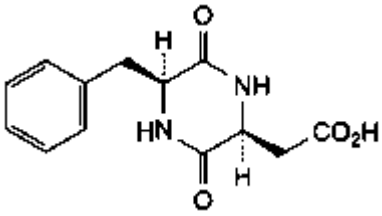
Specified impurities *A, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

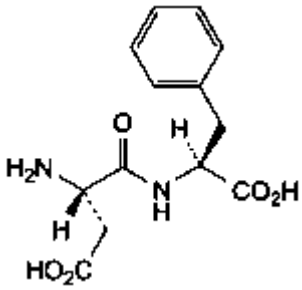
www.webofpharma.com

https://thuocngocanh.com/

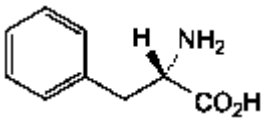
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. 2-[(2*S*,5*S*)-5-benzyl-3,6-dioxopiperazin-2-yl]acetic acid,



B. (3*S*)-3-amino-4-[[(1*S*)-1-carboxy-2-phenylethyl]amino]-4-oxobutanoic acid (α-L-aspartyl-L-phenylalanine),



C. (2*S*)-2-amino-3-phenylpropanoic acid (L-phenylalanine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

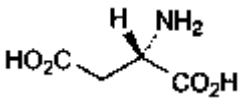
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspartic Acid

General Notices

(Ph. Eur. monograph 0797)



$C_4H_7NO_4$ 133.1 *56-84-8*

Action and use

Amino acid.

Ph Eur

DEFINITION

(2*S*)-2-Aminobutanedioic acid (L-aspartic acid).

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification [carry out either tests A, C or tests C, D.]

Second identification: A, B, E.

A. Specific optical rotation (2.2.7): + 24.0 to + 26.0 (dried substance).

Dissolve 2.00 g in *hydrochloric acid R1* and dilute to 25.0 mL with the same acid.

www.webofpharma.com

https://thuocngocanh.com/

B. A suspension of 1 g in 10 mL of *water R* is strongly acid (*2.2.4*).

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *aspartic acid CRS*.

D. Enantiomeric purity (see Tests).

E. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in 2 mL of *dilute ammonia R1* and dilute to 50 mL with *water R*.

Reference solution Dissolve 10 mg of *aspartic acid CRS* in 2 mL of *dilute ammonia R1* and dilute to 50 mL with *water R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 0.5 g in a 103 g/L solution of *hydrochloric acid R* and dilute to 10 mL with the same acid.

Enantiomeric purity

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 0.100 g of *D-aspartic acid R* (impurity I) in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 0.100 g of the substance to be examined in 90 mL of *water R*, add 0.3 mL of reference solution (a) and dilute to 100.0 mL with *water R*.

Reference solution (c) Dilute 0.3 mL of reference solution (a) to 100.0 mL with *water R*.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *L-penicillamine coated silica gel for chiral separations R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *2-propanol R*, 0.5 g/L solution of *copper sulfate pentahydrate R* (5:95 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Relative retention With reference to aspartic acid (retention time = about 12 min): impurity I = about 0.85.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity I and aspartic acid.

Calculation of percentage content:

— for impurity I, use the concentration of impurity I in reference solution (c).

Limit:

— *impurity I*: maximum 0.3 per cent.

Other dicarboxylic acids

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.500 g of the substance to be examined in 2.0 mL of a 618 g/L solution of *hydrochloric acid R* and dilute to 10.0 mL with *water R*.

Reference solution (a) Dissolve 20.0 mg of *malic acid R* (impurity A) in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (b) Dissolve 10.0 mg of *maleic acid R* (impurity H) in *water R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with reference solution (a).

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *water R*.

Reference solution (e) Dissolve 10.0 mg of *fumaric acid R* (impurity B) in *water R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.30 m, Ø = 7.8 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *cation-exchange resin R* (9 µm);

— *temperature*: 30 °C.

Mobile phase 0.39 g/L solution of *sulfuric acid R*.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL.

Run time 4 times the retention time of impurity H.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and H; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity B.

Relative retention With reference to impurity H (retention time = about 7.5 min): impurity A = about 1.2; impurity B = about 2.0.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities H and A.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (d);

— for impurities B and H, use the concentration of impurity H in reference solution (b);

— for impurities other than B and H, use the concentration of impurity A in reference solution (d).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *impurity B*: maximum 0.10 per cent;

— *impurity H*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Ninhydrin-positive substances

Amino acid analysis (*2.2.56*). For analysis, use Method 1.

www.webofpharma.com

https://thuvienthuocngocanh.com/

The concentrations of the test and reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A dilute hydrochloric acid R1 or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of proline R in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of ammonium standard solution (100 ppm NH_4) R to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of isoleucine R and 30 mg of leucine R in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Reference solution (e) Dissolve 30.0 mg of alanine R (impurity D), 60.0 mg of asparagine R (impurity G) and 30.0 mg of glutamic acid R (impurity C) in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test solution, blank solution and reference solutions (a), (b), (d) and (e) into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— resolution: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

— for impurities C, D and G, use the concentration of each impurity in reference solution (e);

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of aspartic acid in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *impurities C, D, G*: for each impurity, maximum 0.2 per cent;

— *any ninhydrin-positive substance*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 200 ppm.

Dissolve 0.25 g in 3 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*. Add 1 mL of *water R* instead of 1 mL of *dilute nitric acid R*.

Sulfates (2.4.13)

Maximum 300 ppm.

Dissolve 0.5 g in 4 mL of *hydrochloric acid R* and dilute to 15 mL with *distilled water R*. Carry out the evaluation of the test after 30 min.

Ammonium

Amino acid analysis (2.2.56) as described in the test for ninhydrin-positive substances with the following modification.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Iron (2.4.9)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. Use the aqueous layer.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 50 mL of *carbon dioxide-free water R*, with slight heating if necessary. Cool and titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M sodium hydroxide* is equivalent to 13.31 mg of $C_4H_7NO_4$.

STORAGE

www.webofpharma.com

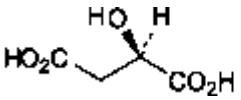
https://thuocngocanh.com/

Protected from light.

IMPURITIES

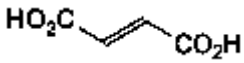
Specified impurities *A, B, C, D, H, G, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F.*

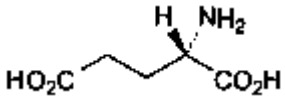


and enantiomer

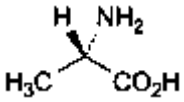
A. (2*RS*)-2-hydroxybutanedioic acid (malic acid),



B. (2*E*)-but-2-enedioic acid (fumaric acid),

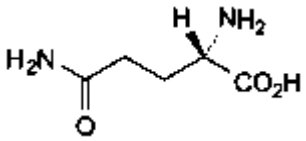


C. (2*S*)-2-aminopentanedioic acid (glutamic acid),

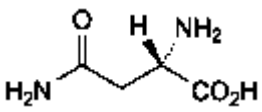


D. (2*S*)-2-aminopropanoic acid (alanine),

E. butanedioic acid (succinic acid),



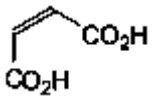
F. (2*S*)-2,5-diamino-5-oxopentanoic acid (L-glutamine),



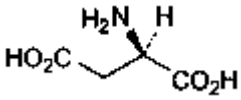
G. (2*S*)-2,4-diamino-4-oxobutanoic acid (asparagine),

www.webofpharma.com

https://thuocngocanh.com/



H. (2*Z*)-but-2-enedioic acid (maleic acid),



I. (2*R*)-2-aminobutanedioic acid (D-aspartic acid).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

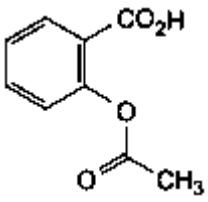
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspirin

General Notices

(Acetylsalicylic Acid, Ph. Eur. monograph 0309)



$C_9H_8O_4$ 180.2 *50-78-2*

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

Preparations

Aspirin Tablets

Aspirin Dispersible Tablets

Aspirin Effervescent Soluble Tablets

Aspirin Gastro-resistant Tablets

Aspirin and Caffeine Tablets

Co-codaprin Tablets

Co-codaprin Dispersible Tablets

Ph Eur

DEFINITION

2-(Acetyloxy)benzoic acid.

Content

99.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent).

mp

About 143 °C (instantaneous method).

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *acetylsalicylic acid CRS*.

B. To 0.2 g add 4 mL of *dilute sodium hydroxide solution R* and boil for 3 min. Cool and add 5 mL of *dilute sulfuric acid R*. A crystalline precipitate is formed. Filter, wash the precipitate and dry at 100-105 °C. The melting point (2.2.14) is 156 °C to 161 °C.

C. In a test tube mix 0.1 g with 0.5 g of *calcium hydroxide R*. Heat the mixture and expose to the fumes produced a piece of filter paper impregnated with 0.05 mL of *nitrobenzaldehyde solution R*. A greenish-blue or greenish-yellow colour develops on the paper. Moisten the paper with *dilute hydrochloric acid R*. The colour becomes blue.

D. Dissolve with heating about 20 mg of the precipitate obtained in identification test B in 10 mL of *water R* and cool. The solution gives reaction (a) of salicylates (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 1.0 g in 9 mL of *ethanol (96 per cent) R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 0.100 g of the substance to be examined in *acetonitrile for chromatography R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of *salicylic acid R* (impurity C) in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 10 mg of *salicylic acid R* (impurity C) in the mobile phase and dilute to 10.0 mL with the mobile phase. To 1.0 mL of the solution add 0.2 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve with the aid of ultrasound the contents of a vial of *acetylsalicylic acid for peak identification CRS* (containing impurities A, B, D, E and F) in 1.0 mL of *acetonitrile R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *phosphoric acid R*, *acetonitrile for chromatography R*, *water R* (2:400:600 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 237 nm.

Injection 10 µL.

Run time 7 times the retention time of acetylsalicylic acid.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C; use the chromatogram supplied with *acetylsalicylic acid for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, D, E and F.

Relative retention With reference to acetylsalicylic acid (retention time = about 5 min): impurity A = about 0.7; impurity B = about 0.8; impurity C = about 1.3; impurity D = about 2.3; impurity E = about 3.2; impurity F = about 6.0.

System suitability Reference solution (b):

— *resolution*: minimum 6.0 between the peaks due to acetylsalicylic acid and impurity C.

Limits:

— *impurities A, B, C, D, E, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In a flask with a ground-glass stopper, dissolve 1.000 g in 10 mL of *ethanol (96 per cent) R*. Add 50.0 mL of *0.5 M sodium hydroxide*. Close the flask and allow to stand for 1 h. Using 0.2 mL of *phenolphthalein solution R* as indicator, titrate with *0.5 M hydrochloric acid*. Carry out a blank titration.

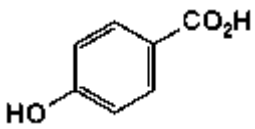
1 mL of *0.5 M sodium hydroxide* is equivalent to 45.04 mg of $C_9H_8O_4$.

STORAGE

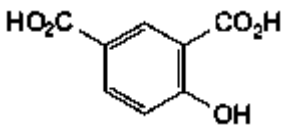
In an airtight container.

IMPURITIES

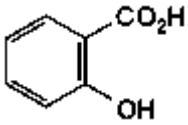
Specified impurities *A, B, C, D, E, F.*



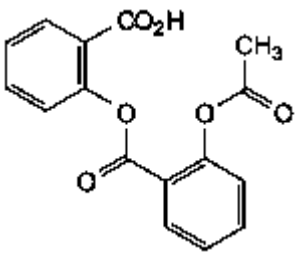
A. 4-hydroxybenzoic acid,



B. 4-hydroxybenzene-1,3-dicarboxylic acid (4-hydroxyisophthalic acid),



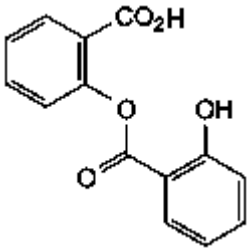
C. 2-hydroxybenzenecarboxylic acid (salicylic acid),



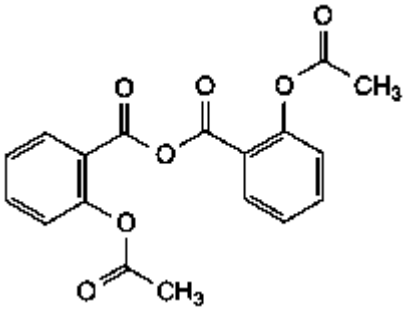
D. 2-[[2-(acetyloxy)benzoyl]oxy]benzoic acid (acetylsalicylsalicylic acid),

www.webofpharma.com

https://thuocngocanh.com/



E. 2-[(2-hydroxybenzoyl)oxy]benzoic acid (salsalate, salicylsalicylic acid),



F. 2-(acetyloxy)benzoic anhydride (acetylsalicylic anhydride).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspirin and Caffeine Tablets

General Notices

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

DEFINITION

Aspirin and Caffeine Tablets contain, in each, 350 mg of Aspirin and 30 mg of Caffeine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aspirin, $C_9H_8O_4$

330 to 370 mg.

Content of caffeine, $C_8H_{10}N_4O_2$

27.5 to 32.5 mg.

IDENTIFICATION

A. Boil 1 g of the powdered tablets with 10 mL of 1M *sodium hydroxide*, cool and filter. Acidify the filtrate with 1M *sulfuric acid*; a white precipitate is produced. To a solution of the precipitate add *iron(III) chloride solution R1*; a deep violet colour is produced.

B. Shake 0.5 g of the powdered tablets with 10 mL of *water* for 5 minutes, filter and add 10 mL of 1M *sodium hydroxide*. Extract with three 30 mL quantities of *dichloromethane*, washing each extract with the same 10 mL of *water*. Filter the combined extracts through absorbent cotton and evaporate the filtrate to dryness. Reserve a quantity of the residue for test C. Dissolve 10 mg of the residue in 1 mL of *hydrochloric acid*, add 0.1 g of *potassium chlorate* and evaporate to dryness in a porcelain dish. A reddish residue remains, which becomes purple on exposure to ammonia vapour.

C. The *light absorption*, Appendix II B, in the range 240 to 350 nm of a 0.001% w/v solution of the residue reserved in test B exhibits a maximum at 273 nm.

TESTS

Salicylic acid

To a quantity of the powdered tablets containing 0.50 g of Aspirin add 50 mL of *dichloromethane* and 10 mL of *water*, shake well and allow to separate. Filter the dichloromethane layer through a dry filter paper and evaporate 10 mL of the filtrate to dryness at room temperature using a rotary evaporator. To the residue add 4 mL of *ethanol (96%)*, stir well, dilute to 100 mL with *water* at a temperature not exceeding 10°, filter immediately, rapidly transfer 50 mL to a *Nessler cylinder*, add 1 mL of freshly prepared *ammonium iron(III) sulfate solution R1*, mix

www.webofpharma.com

https://thuocngocanh.com/

and allow to stand for 1 minute. Any violet colour produced is not more intense than that obtained by adding 1 mL of freshly prepared *ammonium iron(III) sulfate solution R1* to a mixture of 3 mL of a freshly prepared 0.050% w/v solution of *salicylic acid* in *ethanol (96%)* and sufficient *water* to produce 50 mL contained in a second *Nessler cylinder* (3.0%).

Dissolution

For aspirin

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 500 mL of a pH 4.5 buffer prepared by mixing 29.9 g of *sodium acetate* and 16.6 mL of *glacial acetic acid* with sufficient *water* to produce 10 litres, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 20 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 265 nm, Appendix II B, using dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *aspirin BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of aspirin, $C_9H_8O_4$, in the medium from the absorbances obtained and using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

ASSAY

Weigh and powder 20 tablets.

For aspirin

To a quantity of the powder containing 0.7 g of Aspirin add 20 mL of *water* and 2 g of *sodium citrate* and boil under a reflux condenser for 30 minutes. Cool, wash the condenser with 30 mL of warm *water* and titrate with *0.5M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *0.5M sodium hydroxide VS* is equivalent to 45.04 mg of $C_9H_8O_4$.

For caffeine

To a quantity of the powder containing 30 mg of Caffeine add 200 mL of *water* and shake for 30 minutes. Add sufficient *water* to produce 250 mL and filter. To 10 mL of the filtrate add 10 mL of 1M *sodium hydroxide* and extract immediately with five 30 mL quantities of *chloroform*, washing each extract with the same 10 mL of *water*. Filter the combined chloroform extracts, if necessary, through absorbent cotton previously moistened with *chloroform*. Evaporate the solution to dryness and dissolve the residue as completely as possible in *water*, warming gently if necessary. Cool, add sufficient *water* to produce 100 mL, mix and filter if necessary. Measure the *absorbance* of the

www.webofpharma.com

https://thuocngocanh.com/

resulting solution at the maximum at 273 nm, Appendix II B. Calculate the content of $C_8H_{10}N_4O_2$ taking 504 as the value of A(1%, 1 cm) at the maximum at 273 nm.

LABELLING

The label states that the tablets contain Aspirin, unless this word appears in the name of the tablets. This requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspirin Dispersible Tablets

General Notices

Dispersible Aspirin Tablets

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

DEFINITION

Aspirin Dispersible Tablets contain Aspirin in a suitable dispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aspirin, $C_9H_8O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Aspirin with 20 mL of *absolute ethanol*, filter (Whatman GF/C is suitable), evaporate the filtrate and dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, is concordant with the *reference spectrum* of aspirin *(RS 483)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 0.10 g of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.
(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase and further dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(3) 0.003% w/v of *salicylic acid* (impurity C) in the mobile phase.
(4) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 237 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 1.2 times the retention time of impurity F.

MOBILE PHASE

2 volumes of *orthophosphoric acid*, 400 volumes of *acetonitrile* and 600 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retentions relative to aspirin (retention time about 5 minutes) are: impurity A, about 0.6; impurity B, about 0.7, impurity C, about 1.4 and impurity F, about 8.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4) the *resolution* between the peaks due to aspirin and impurity C is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 60 mg of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.

(2) 0.06% w/v of *aspirin BPCRS* in the mobile phase.

(3) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuvienthuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to aspirin and impurity C is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_8O_4$ in the tablets from the chromatograms obtained using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

LABELLING

The label states that the tablets contain Aspirin, unless this word appears in the name of the tablets (this requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed).

When Aspirin Dispersible Tablets are prescribed or demanded, no strength being stated, tablets containing 300 mg shall be dispensed or supplied.

When Aspirin Soluble tablets are prescribed, Aspirin Dispersible Tablets shall be dispensed.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aspirin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspirin Effervescent Soluble Tablets

General Notices

Effervescent Aspirin Tablets

Effervescent Soluble Aspirin Tablets

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

DEFINITION

Aspirin Effervescent Soluble Tablets contain Aspirin in a suitable soluble, effervescent basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aspirin, $C_9H_8O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve with vigorous effervescence on the addition of warm *water* to produce a clear solution.

B. Dissolve a quantity of the powdered tablets containing 50 mg of Aspirin in 10 mL of warm *water*, boil and add 0.5 mL of *iron(III) chloride solution R1*. A violet-red colour is produced.

TESTS

Disintegration

Comply with the requirement for Effervescent Tablets stated under Tablets.

Salicylic acid

To a quantity of the powdered tablets containing 0.50 g of Aspirin add 50 mL of *dichloromethane*, 2 mL of 2.5M *sulfuric acid* and shake vigorously for 2 minutes. Filter the dichloromethane extract through a dry filter paper containing 1 g of *anhydrous sodium sulfate* and evaporate 5 mL of the filtrate to dryness at room temperature using a rotary evaporator. Dissolve the residue in 2 mL of *ethanol (96%)*, transfer to a *Nessler cylinder* with a further 1 mL of *ethanol (96%)*, dilute to 50 mL with *water* at a temperature not exceeding 10°, add 1 mL of freshly prepared *ammonium iron(III) sulfate solution R1*, mix and allow to stand for 1 minute. Any violet colour produced is not more intense than that obtained by adding 1 mL of freshly prepared *ammonium iron(III) sulfate solution R1* to a mixture of 3 mL of a freshly prepared 0.050% w/v solution of *salicylic acid* in *ethanol (96%)* and sufficient *water* to produce 50 mL contained in a second *Nessler cylinder* (3.0%).

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.3 g of Aspirin in 10 mL of 1M *sulfuric acid* and boil under a reflux condenser for 1 hour. Cool, transfer to a separating funnel, rinsing the flask and condenser with small quantities of *water* and extract the liberated salicylic acid with four 20-mL quantities of *ether*. Wash the combined ether extracts with two 5-mL quantities of *water*, evaporate the ether in a current of air at a temperature not exceeding 30°, dissolve the residue in 20 mL of *0.5M sodium hydroxide VS* and dilute to 200 mL with *water*. Transfer 50 mL to a stoppered flask, add 50 mL of *0.05M bromine VS* and 5 mL of *hydrochloric acid*, protect the solution from light, shake repeatedly during 15 minutes and allow to stand for 15 minutes. Add 20-mL of *dilute potassium iodide solution* shake thoroughly and titrate with 0.1M *sodium thiosulfate VS*, using *starch mucilage*, added towards the end point, as indicator. Each mL of *0.05M bromine VS* is equivalent to 3.003 mg of $C_9H_8O_4$.

LABELLING

The label states that the tablets contain Aspirin, unless this word appears in the name of the tablets (this requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed).

When Aspirin Effervescent Soluble Tablets are prescribed or demanded, no strength being stated, tablets containing 300 mg shall be dispensed or supplied.

When Aspirin Soluble tablets are prescribed, Aspirin Dispersible Tablets shall be dispensed.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspirin Gastro-resistant Tablets

General Notices

Gastro-resistant Aspirin Tablets

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

DEFINITION

Aspirin Gastro-resistant Tablets contain Aspirin. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aspirin, $C_9H_8O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Aspirin with 20 mL of *absolute ethanol*, filter (Whatman GF/C is suitable), evaporate the filtrate and dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, is concordant with the *reference spectrum* of aspirin *(RS 483)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

First stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 1000 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 2 hours, withdraw a sample of the medium, filter and measure the *absorbance* of the filtrate, Appendix II B, at 276 nm using 0.1M *hydrochloric acid* in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *aspirin BPCRS* in 0.1M *hydrochloric acid*.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of aspirin, $C_9H_8O_4$, in the medium using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*. The amount of aspirin released is not more than 5% of the stated amount.

Final stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Replace the 0.1M *hydrochloric acid* in the vessel with 900 mL of *mixed phosphate buffer pH 6.8*, previously held at 36.5° to 37.5°.

PROCEDURE

(1) After 45 minutes, withdraw a sample of the medium and filter. Immediately measure the *absorbance* of the filtrate, Appendix II B, diluted with the dissolution medium, if necessary, at 265 nm using dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *aspirin BPCRS* in the dissolution medium.

DETERMINATION OF CONTENT

Calculate the total content of aspirin, $C_9H_8O_4$, in the medium using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 0.10 g of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.
(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(3) 0.003% w/v of *salicylic acid* (impurity C) in the mobile phase.
(4) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 237 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 1.2 times the retention time of impurity F.

MOBILE PHASE

2 volumes of *orthophosphoric acid*, 400 volumes of *acetonitrile* and 600 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to aspirin (retention time about 5 minutes) are: impurity A, about 0.6; impurity B, about 0.7, impurity C, about 1.4 and impurity F, about 8.0.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (4) the *resolution* between the peaks due to aspirin and impurity C is at least 6.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%);

the area of any other *secondary peak* is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *Liquid Chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 60 mg of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.
(2) 0.06% w/v of *aspirin BPCRS* in the mobile phase.
(3) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to aspirin and impurity C is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_8O_4$ in the tablets from the chromatograms obtained using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

STORAGE

Aspirin Gastro-resistant Tablets should be protected from moisture.

LABELLING

The label states that the tablets contain Aspirin, unless this word appears in the name of the tablets (this requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed).

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aspirin.

© Crown Copyright 2022

www.webofpharma.com

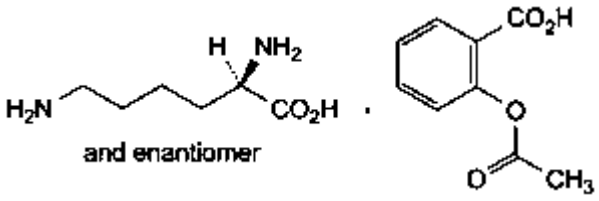
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspirin Lysine

General Notices

(DL-Lysine Acetylsalicylate, Ph. Eur. monograph 2812)



$C_{15}H_{22}N_2O_6$ 326.3 *62952-06-1*

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

(2*RS*)-2,6-Diaminohexanoic acid 2-(acetyloxy)benzoate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Very soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison: *DL-lysine acetylsalicylate CRS*.

TESTS

https://thuocngocanh.com/

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 6.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture Mobile phase B, mobile phase A (10:90 *V/V*).

Solution A Dilute 30 mL of a 103 g/L solution of *hydrochloric acid R* to 1000 mL with the solvent mixture.

Test solution Dissolve 0.100 g of the substance to be examined in 20 mL of solution A and dilute to 25.0 mL with solution A.

Reference solution (a) Dissolve 50 mg of *acetylsalicylic acid R* in 2 mL of *acetonitrile R* and dilute to 50 mL with solution A.

Reference solution (b) Dissolve 0.100 g of *lysine hydrochloride R* in solution A, add 0.5 mL of reference solution (a) and dilute to 50 mL with solution A.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (d) Dissolve 2 mg of *DL-lysine acetylsalicylate impurity C CRS* in solution A and dilute to 50 mL with solution A.

Reference solution (e) Dissolve 2 mg of *DL-lysine acetylsalicylate impurity G CRS* in solution A and dilute to 10 mL with solution A.

Reference solution (f) To 3 mL of reference solution (d) add 1 mL of reference solution (e) and dilute to 10 mL with solution A.

Reference solution (g) Dissolve 5 mg of *N-(ε)-acetyl-L-lysine R* (1 enantiomer of impurity E) and 5 mg of *N-(α)-acetyl-L-lysine R* (1 enantiomer of impurity F) in solution A and dilute to 10 mL with solution A. Dilute 1 mL of the solution to 20 mL with solution A.

Reference solution (h) Dissolve 20.0 mg of *salicylic acid R* (impurity A) in a mixture of equal volumes of *acetonitrile R* and solution A and dilute to 5.0 mL with the same mixture of solvents. Dilute 1.0 mL of the solution to 100.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped amidohexadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: 0.55 g/L solution of *sodium octanesulfonate R* adjusted to pH 2.7 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	92	8
2 - 22	92 → 73	8 → 27
22 - 45	73 → 45	27 → 55

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL of the test solution and reference solutions (b), (c), (f), (g) and (h).

Identification of impurities Use the chromatogram obtained with reference solution (h) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (f) to identify the peaks due to impurities C and G; use the chromatogram obtained with reference solution (g) to identify the peaks due to impurities E and F.

Relative retention With reference to acetylsalicylic acid (retention time = about 11 min): impurity G = about 0.2; impurity E = about 0.3; impurity F = about 0.4; DL-lysine = about 0.9; impurity A = about 1.4; impurity C = about 1.7.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to lysine and acetylsalicylic acid in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 200 for the principal peak in the chromatogram obtained with reference solution (c).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 4.3; impurity E = 3.4; impurity F = 4.3; impurity G = 2.8;

— for impurity A, use the concentration of salicylic acid in reference solution (h);

— for impurities other than A, use the concentration of DL-lysine acetylsalicylate in reference solution (c) taking into account the area of the peak due to acetylsalicylic acid in reference solution (c).

Limits:

— *impurity A*: maximum 1.2 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *impurities E, F, G*: for each impurity, maximum 0.5 per cent;

— *impurity C*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.03 per cent; disregard the peak due to DL-lysine.

Water (2.5.32)

Maximum 0.3 per cent, determined on 0.300 g using the evaporation technique at 100 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

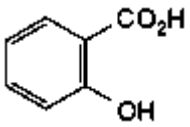
Dissolve 0.140 g in 50.0 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 16.32 mg of $C_{15}H_{22}N_2O_6$.

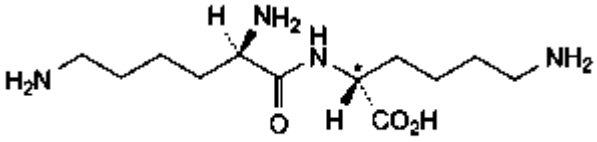
IMPURITIES

Specified impurities *A, C, E, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, H, I, J, K, L, M.*



A. 2-hydroxybenzoic acid (salicylic acid),

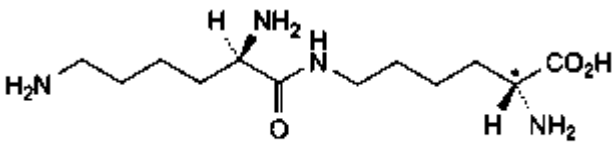


its epimer at C* and their enantiomers

B. (2*RS*)-6-amino-2-[(2*R*)-2,6-diaminohexanamido]hexanoic acid and (2*RS*)-6-amino-2-[(2*S*)-2,6-diaminohexanamido]hexanoic acid,

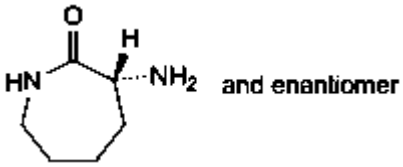
www.webofpharma.com

https://thuocngocanh.com/



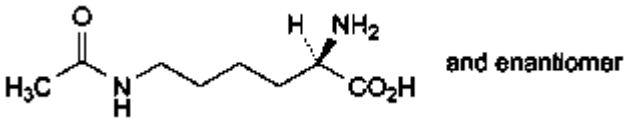
its epimer at C* and their enantiomers

C. (2*RS*)-2-amino-6-[(2*R*)-2,6-diaminohexanamido]hexanoic acid and (2*RS*)-2-amino-6-[(2*S*)-2,6-diaminohexanamido]hexanoic acid,



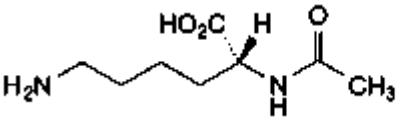
and enantiomer

D. (3*RS*)-3-aminoazepan-2-one,



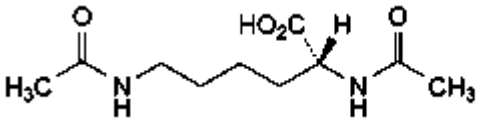
and enantiomer

E. (2*RS*)-6-acetamido-2-aminohexanoic acid (*N*-(ε)-acetyl-DL-lysine),



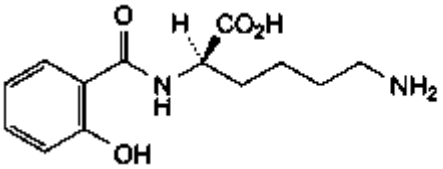
and enantiomer

F. (2*RS*)-2-acetamido-6-aminohexanoic acid (*N*-(α)-acetyl-DL-lysine),



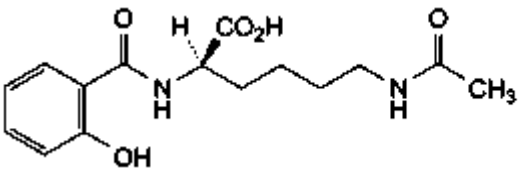
and enantiomer

G. (2*RS*)-2,6-diacetamidohexanoic acid,



and enantiomer

H. (2*RS*)-6-amino-2-(2-hydroxybenzamido)hexanoic acid,

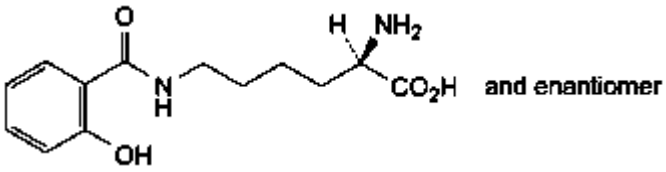


and enantiomer

I. (2*RS*)-6-acetamido-2-(2-hydroxybenzamido)hexanoic acid,

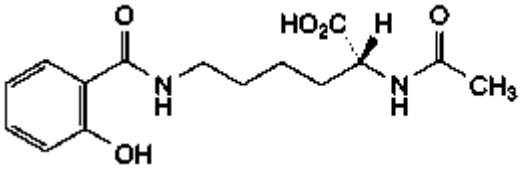
www.webofpharma.com

https://thuocngocanh.com/



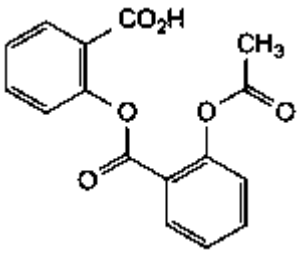
and enantiomer

J. (2*RS*)-2-amino-6-(2-hydroxybenzamido)hexanoic acid,

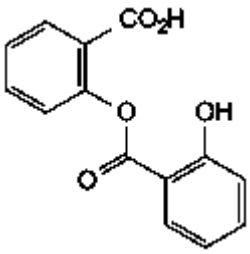


and enantiomer

K. (2*RS*)-2-acetamido-6-(2-hydroxybenzamido)hexanoic acid,



L. 2-[[2-(acetyloxy)benzoyl]oxy]benzoic acid (acetylsalicylsalicylic acid),



M. 2-[(2-hydroxybenzoyl)oxy]benzoic acid (salsalate, salicylsalicylic acid).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspirin Tablets

General Notices

Acetylsalicylic Acid Tablets

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

DEFINITION

Aspirin Tablets contain Aspirin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aspirin, $C_9H_8O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Aspirin with 20 mL of *absolute ethanol*, filter (Whatman GF/C is suitable), evaporate the filtrate and dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, is concordant with the *reference spectrum* of aspirin *(RS 483)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.
(b) Use 500 mL of a pH 4.5 buffer prepared by mixing 29.9 g of *sodium acetate* and 16.6 mL of *glacial acetic acid* with sufficient *water* to produce 10 litres at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 265 nm, Appendix II B using dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *aspirin BPCRS* using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of aspirin, $C_9H_8O_4$, in the medium using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 0.10 g of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(3) 0.003% w/v of *salicylic acid* (impurity C) in the mobile phase.

(4) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 237 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.2 times the retention time of impurity F.

MOBILE PHASE

2 volumes of *orthophosphoric acid*, 400 volumes of *acetonitrile* and 600 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to aspirin (retention time about 5 minutes) are: impurity A, about 0.6; impurity B, about 0.7, impurity C, about 1.4 and impurity F, about 8.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4) the *resolution* between the peaks due to aspirin and impurity C is at least 6.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%);

the area of any other *secondary peak* is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

www.webofpharma.com

https://thuocngocanh.com/

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 60 mg of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.

(2) 0.06% w/v of *aspirin BPCRS* in the mobile phase.

(3) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to aspirin and impurity C is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_8O_4$ in the tablets from the chromatograms obtained using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

LABELLING

The label states that the tablets contain Aspirin, unless this word appears in the name of the tablets. This requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aspirin.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

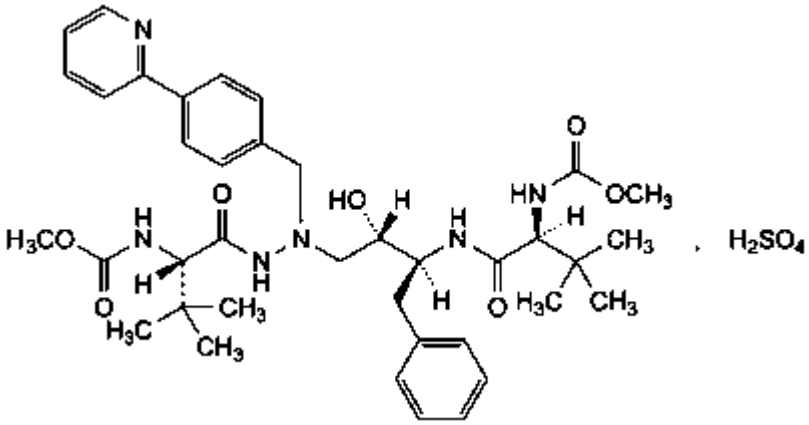
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atazanavir Sulfate

General Notices

(Ph. Eur. monograph 2898)



$C_{38}H_{54}N_6O_{11}S$ 803 *229975-97-7*

Action and use

Antiviral (HIV).

Ph Eur

DEFINITION

Methyl [(5*S*,10*S*,11*S*,14*S*)-11-benzyl-5-*tert*-butyl-10-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-[[4-(pyridin-2-yl)phenyl]methyl]-2-oxa-4,7,8,12-tetraazahexadecan-14-yl]carbamate sulfate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow, slightly hygroscopic, crystalline powder that may contain agglomerates.

Solubility

Slightly soluble in water, freely soluble in ethanol (96 per cent), practically insoluble in heptane.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *atazanavir sulfate CRS*.

C. It gives reaction (a) of sulfates (2.3.1).

TESTS

Specific optical rotation (2.2.7)

-44 to -40 (anhydrous substance), measured at 25 °C.

Dissolve 0.100 g in 8 mL of *methanol R*, using sonication if necessary, and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mix equal volumes of *acetonitrile R1* and a freshly prepared 2.73 g/L solution of *potassium dihydrogen phosphate R* in *water for chromatography R* previously adjusted to pH 3.5 with *dilute phosphoric acid R*.

Test solution (a) Dissolve 20.0 mg of the substance to be examined in 40 mL of the solvent mixture, sonicate for 3 min and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in 40 mL of the solvent mixture, sonicate for 3 min and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 20.0 mg of *atazanavir sulfate CRS* in 40 mL of the solvent mixture, sonicate for 3 min and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 4 mg of *atazanavir for system suitability CRS* (containing impurity F) in 8 mL of the solvent mixture, sonicate for 3 min and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 2.0 mg of *atazanavir impurity K CRS* in 9 mL of the solvent mixture, sonicate for 3 min and dilute to 10.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 100.0 mL with the solvent mixture. Dilute 3.0 mL of this solution to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.0 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: mix 25 volumes of *acetonitrile R1* and 75 volumes of a freshly prepared 2.73 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.5 with *dilute phosphoric acid R*;

— *mobile phase B*: mix 25 volumes of a freshly prepared 2.73 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.5 with *dilute phosphoric acid R*, and 75 volumes of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 45	100 → 0	0 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL of test solution (a) and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *atazanavir for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity F.

Relative retention With reference to atazanavir (retention time = about 30 min): impurity F = about 0.99.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity F and atazanavir.

Calculation of percentage contents:

— for each impurity, use the concentration of atazanavir sulfate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak with a relative retention with reference to atazanavir of less than 0.2.

Impurity K

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 8	95 → 0	5 → 100
8 - 14	0	100

Injection 20 µL of test solution (b) and reference solution (d).

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity K.

Relative retention With reference to atazanavir (retention time = about 10 min): impurity K = about 0.4.

Calculation of percentage content:

— for impurity K, use the concentration of impurity K in reference solution (d).

Limit:

— *impurity K*: maximum 0.15 per cent.

Water (*2.5.32*)

Maximum 2.5 per cent, determined on 0.100 g by direct sample introduction.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Solvent mixture.

Injection Test solution (a) and reference solutions (a) and (c).

Run time 1.6 times the retention time of atazanavir.

Relative retention With reference to atazanavir (retention time = about 9.5 min): impurity F = about 0.94.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity F and atazanavir.

Calculate the percentage content of $C_{38}H_{54}N_6O_{11}S$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *atazanavir sulfate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

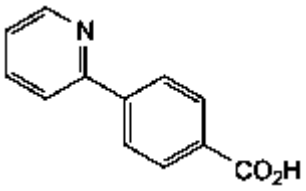
STORAGE

In an airtight container.

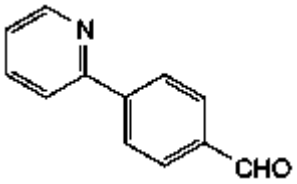
IMPURITIES

Specified impurities K.

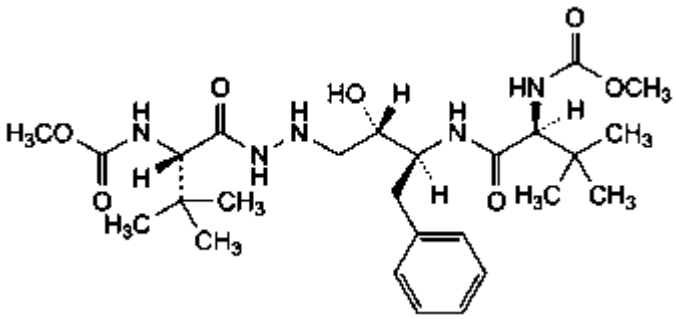
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I, J.



A. 4-(pyridin-2-yl)benzoic acid,



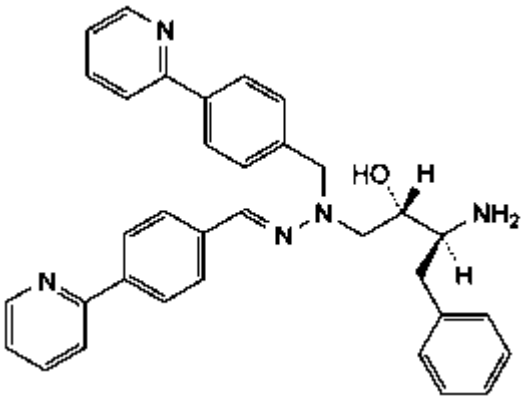
B. 4-(pyridin-2-yl)benzaldehyde,



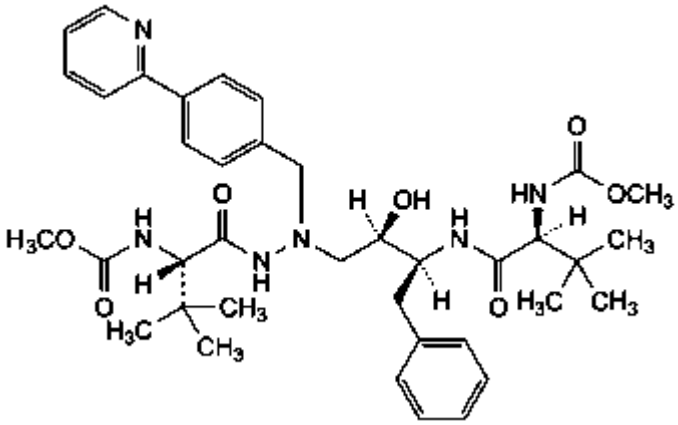
C. methyl [(5*S*,10*S*,11*S*,14*S*)-11-benzyl-5-*tert*-butyl-10-hydroxy-15,15-dimethyl-3,6,13-trioxo-2-oxa-4,7,8,12-tetraazahexadecan-14-yl]carbamate,

www.webofpharma.com

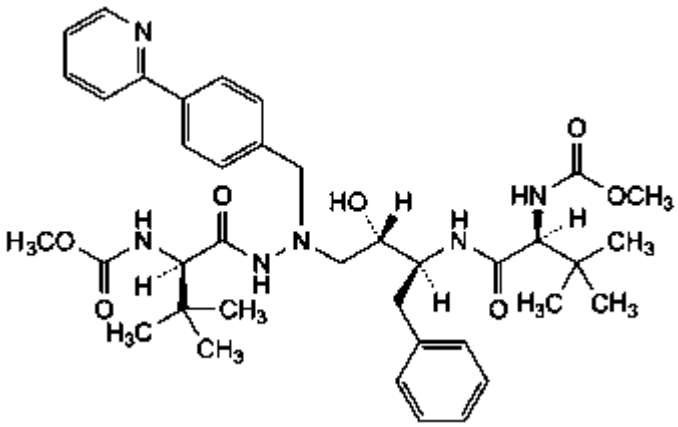
https://thuocngocanh.com/



D. (2*S*,3*S*)-3-amino-4-phenyl-1-[(*E*)-1-[[4-(pyridin-2-yl)phenyl]methyl]-2-[[4-(pyridin-2-yl)phenyl]methylidene]hydrazin-1-yl]butan-2-ol,



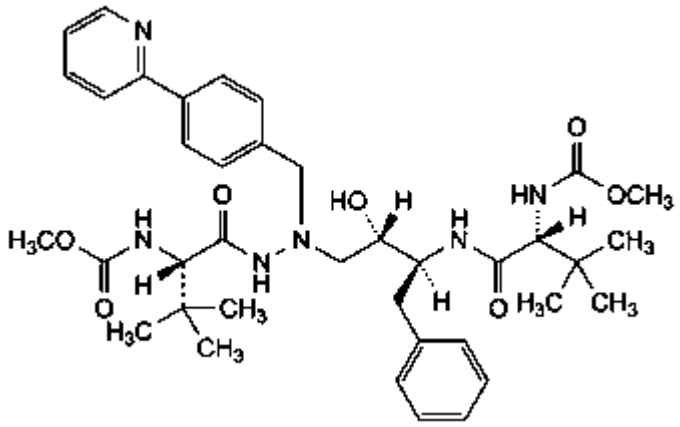
E. methyl [(5*S*,10*R*,11*S*,14*S*)-11-benzyl-5-*tert*-butyl-10-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-[[4-(pyridin-2-yl)phenyl]methyl]-2-oxa-4,7,8,12-tetraazahexadecan-14-yl]carbamate,



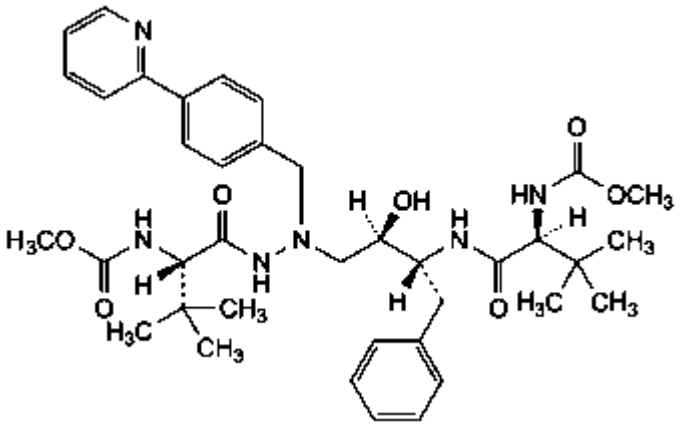
F. methyl [(5*R*,10*S*,11*S*,14*S*)-11-benzyl-5-*tert*-butyl-10-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-[[4-(pyridin-2-yl)phenyl]methyl]-2-oxa-4,7,8,12-tetraazahexadecan-14-yl]carbamate,

www.webofpharma.com

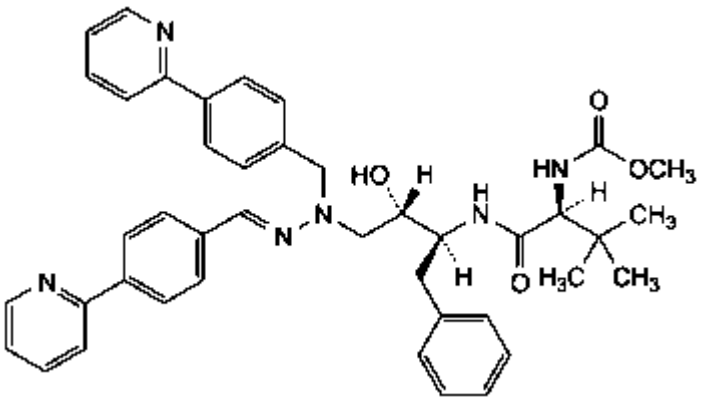
https://thuocngocanh.com/



G. methyl [(5*S*,10*S*,11*S*,14*R*)-11-benzyl-5-*tert*-butyl-10-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-[[4-(pyridin-2-yl)phenyl]methyl]-2-oxa-4,7,8,12-tetraazahexadecan-14-yl]carbamate,



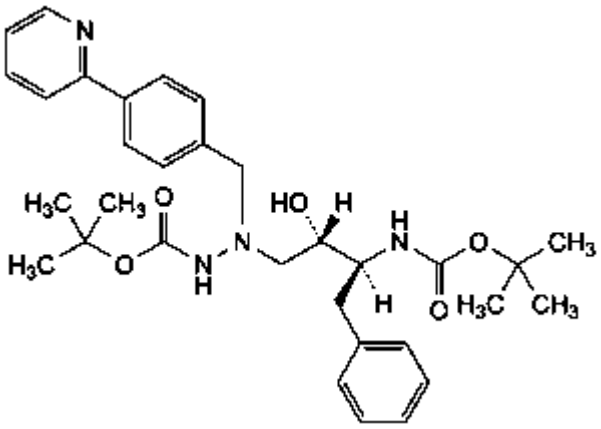
H. methyl [(5*S*,10*R*,11*R*,14*S*)-11-benzyl-5-*tert*-butyl-10-hydroxy-15,15-dimethyl-3,6,13-trioxo-8-[[4-(pyridin-2-yl)phenyl]methyl]-2-oxa-4,7,8,12-tetraazahexadecan-14-yl]carbamate,



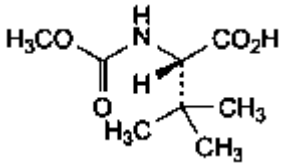
I. methyl [(2*S*)-1-[[(2*S*,3*S*)-3-hydroxy-1-phenyl-4-[(*E*)-1-[[4-(pyridin-2-yl)phenyl]methyl]-2-[[4-(pyridin-2-yl)phenyl]methylidene]hydrazin-1-yl]butan-2-yl]amino]-3,3-dimethyl-1-oxobutan-2-yl]carbamate,

www.webofpharma.com

https://thuocngocanh.com/



J. *tert*-butyl 2-[(2*S*,3*S*)-3-(*tert*-butoxyformamido)-2-hydroxy-4-phenylbutyl]-2-[[4-(pyridin-2-yl)phenyl]methyl]hydrazine-1-carboxylate,



K. (2*S*)-2-(methoxyformamido)-3,3-dimethylbutanoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

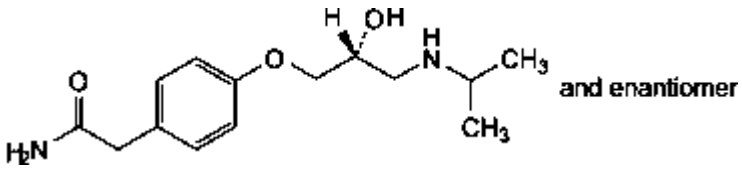
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atenolol

General Notices

(Ph. Eur. monograph 0703)



$C_{14}H_{22}N_2O_3$ 266.3 *29122-68-7*

Action and use

Beta-adrenoceptor antagonist.

Preparations

Atenolol Injection

Atenolol Oral Solution

Atenolol Tablets

Co-tenidone Tablets

Ph Eur

DEFINITION

2-[4-[(2*RS*)-2-Hydroxy-3-[(propan-2-yl)amino]propoxy]phenyl]acetamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Sparingly soluble in water, soluble in anhydrous ethanol, slightly soluble in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (*2.2.14*): 152 °C to 155 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *atenolol CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in 1.0 mL of *methanol R*.

Reference solution Dissolve 10 mg of *atenolol CRS* in 1.0 mL of *methanol R*.

Plate *TLC silanised silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R1*, *methanol R* (1:99 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 0.10 g in *water R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in 20 mL of the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of atenolol for system suitability CRS (containing impurities B, F, G, I and J) in 1 mL of the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Dissolve 1.0 g of sodium octanesulfonate R and 0.4 g of tetrabutylammonium hydrogen sulfate R in 1000 mL of a mixture of 20 volumes of tetrahydrofuran R, 180 volumes of methanol R2 and 800 volumes of a 3.4 g/L solution of potassium dihydrogen phosphate R; adjust the apparent pH to 3.0 with phosphoric acid R.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 226 nm.

Injection 10 µL.

Run time 5 times the retention time of atenolol.

Identification of impurities Use the chromatogram supplied with atenolol for system suitability CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, F, G, I and J.

Relative retention With reference to atenolol (retention time = about 8 min): impurity B = about 0.3; impurity J = about 0.7; impurity I = about 0.8; impurity F = about 2.0 (pair of peaks); impurity G = about 3.5.

System suitability Reference solution (a):

— resolution: minimum 1.4 between the peaks due to impurities J and I.

Limits:

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities F, G, I, J*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides (2.4.4)

Maximum 0.1 per cent.

Dissolve 50 mg in a mixture of 1 mL of *dilute nitric acid R* and 15 mL of *water R*. The solution, without further addition of *dilute nitric acid R*, complies with the test.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

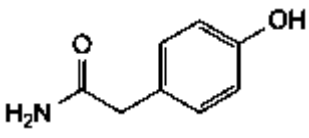
Dissolve 0.200 g in 80 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 26.63 mg of $C_{14}H_{22}N_2O_3$.

IMPURITIES

Specified impurities *B, F, G, I, J.*

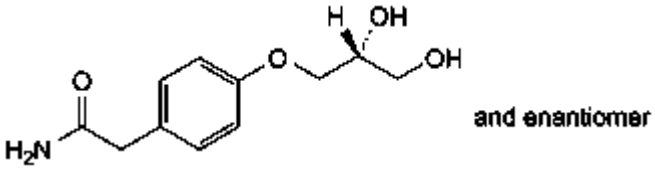
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E, H.*



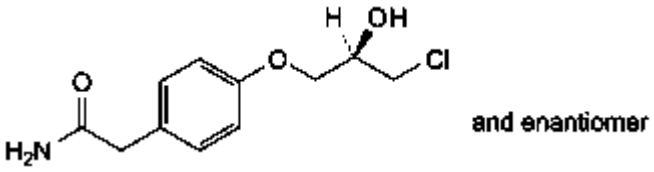
A. 2-(4-hydroxyphenyl)acetamide,

www.webofpharma.com

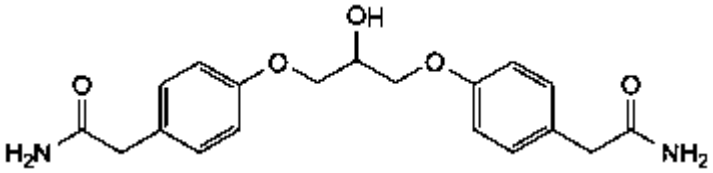
https://thuocngocanh.com/



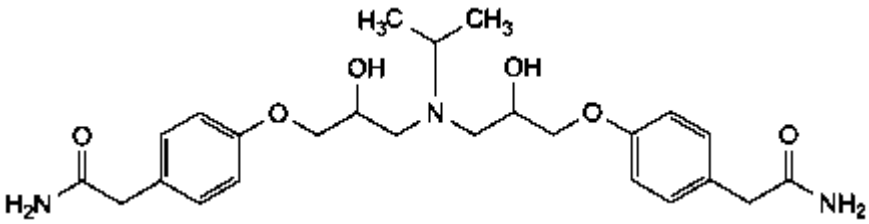
B. 2-[4-[(2*RS*)-2,3-dihydroxypropoxy]phenyl]acetamide,



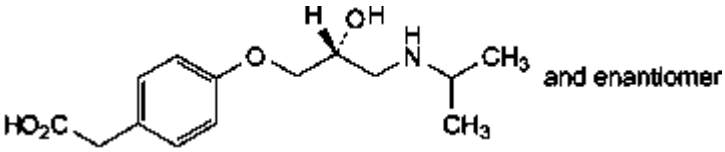
D. 2-[4-[(2*RS*)-3-chloro-2-hydroxypropoxy]phenyl]acetamide,



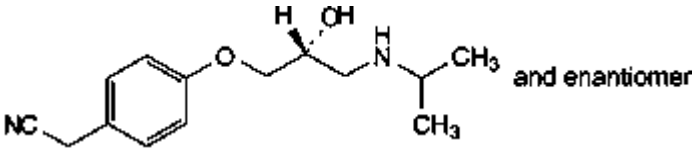
E. 2,2′-[(2-hydroxypropane-1,3-diyl)bis(oxy-4,1-phenylene)]diacetamide,



F. 2,2′-[[(propan-2-yl)azanediyl]bis[(2-hydroxypropane-3,1-diyl)oxy-4,1-phenylene]]diacetamide,



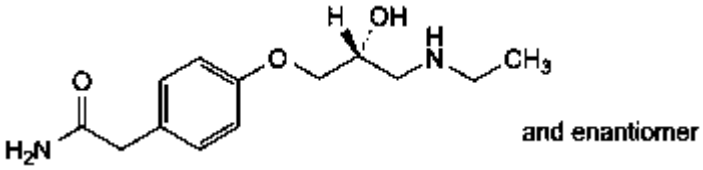
G. [4-[(2*RS*)-2-hydroxy-3-[(propan-2-yl)amino]propoxy]phenyl]acetic acid,



H. [4-[(2*RS*)-2-hydroxy-3-[(propan-2-yl)amino]propoxy]phenyl]acetonitrile,

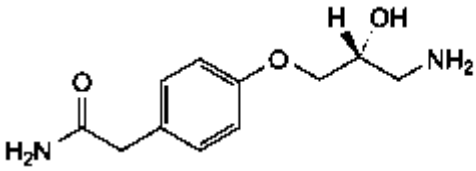
www.webofpharma.com

https://thuocngocanh.com/



and enantiomer

I. 2-[4-[(2*RS*)-3-(ethylamino)-2-hydroxypropoxy]phenyl]acetamide,



and enantiomer

J. 2-[4-[(2*RS*)-3-amino-2-hydroxypropoxy]phenyl]acetamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atenolol Injection

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Atenolol Injection is a sterile solution of Atenolol in Water for Injections containing Citric Acid Monohydrate and Sodium Chloride.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of atenolol, $C_{14}H_{22}N_2O_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

To a volume of the injection containing 5 mg of Atenolol add sufficient 1M *sodium hydroxide* to make it alkaline (about 0.5 mL) and extract with three 10-mL quantities of a mixture of 1 volume of *propan-2-ol* and 3 volumes of *chloroform*. Filter the combined extracts through *anhydrous sodium sulfate* and evaporate to dryness in a current of nitrogen. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of atenolol *(RS 015)*.

TESTS

Acidity

pH, 5.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the injection being examined.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) Dissolve 10 mg of *atenolol impurity standard BPCRS* in 0.1 mL of *dimethyl sulfoxide*, with the aid of gentle heat, and dilute to 20 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Luna-C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of impurity G.

MOBILE PHASE

20 volumes of *tetrahydrofuran*, 180 volumes of *methanol* and 800 volumes of 0.025M *potassium dihydrogen orthophosphate*. Dissolve 0.8 g of *sodium octanesulfonate* and 0.4 g of *tetrabutylammonium hydrogen sulfate* to 1 litre of this solution and adjust the pH to 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles that of the reference chromatogram provided with *atenolol impurity standard BPCRS* in that the peak due to impurity E precedes, and is separated from, that due to impurity F, which is normally a doublet. If necessary adjust the concentration of sodium octanesulfonate in the mobile phase; increasing the concentration increases the retention time of impurity F.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity G is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to either impurity E or impurity F is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.25%).

ASSAY

Dilute a volume of the injection containing 10 mg of Atenolol to 100 mL with *methanol* and measure the *absorbance* at the maximum at about 275 nm, Appendix II B. Calculate the content of $C_{14}H_{22}N_2O_3$ taking 53.7 as the value of A(1%, 1 cm) at the maximum at 275 nm.

STORAGE

Atenolol Injection should be protected from light.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atenolol Oral Solution

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Atenolol Oral Solution is a solution of Atenolol in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of atenolol, $C_{14}H_{22}N_2O_3$

94.0 to 106.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Make a volume of the oral solution containing 50 mg of Atenolol alkaline with 1M *sodium hydroxide* (about 0.5 mL), extract with three 10-mL quantities of a mixture of 1 volume of *propan-2-ol* and 3 volumes of *chloroform*, filter the combined extracts through *anhydrous sodium sulfate*, evaporate to dryness under reduced pressure with gentle heat and dissolve the residue in 0.5 mL of *methanol*.

(2) 1.0% w/v of *atenolol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia* and 99 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, size and intensity to that in the chromatogram obtained with solution (2). Disregard any spots due to excipients at Rf values of 0.69 and 0.80.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as that in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity

pH, 5.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the oral solution with the mobile phase to produce a solution containing 0.2% w/v of Atenolol.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) Dissolve 10 mg of *atenolol impurity standard BPCRS* in 0.1 mL of *dimethyl sulfoxide*, with the aid of gentle heat, and dilute to 20 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of impurity G.

MOBILE PHASE

20 volumes of *tetrahydrofuran*, 180 volumes of *methanol* and 800 volumes of 0.025M *potassium dihydrogen orthophosphate*. Dissolve 0.8 g of *sodium octanesulfonate* and 0.4 g of *tetrabutylammonium hydrogen sulfate* to 1 litre of this solution and adjust the pH to 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles that of the reference chromatogram provided with *atenolol impurity standard BPCRS* in that the peak due to impurity E precedes, and is separated from, that due to impurity F, which is normally a doublet. If necessary adjust the concentration of sodium octanesulfonate in the mobile phase; increasing the concentration increases the retention time of impurity F.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity G is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to either impurity E or impurity F is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.25%).

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the oral solution with the mobile phase to produce a solution containing 0.025% w/v of Atenolol.

(2) 0.025% w/v of *atenolol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for at least 30 minutes.

MOBILE PHASE

1 volume of *sulfuric acid (10%)*, 25 volumes of *acetonitrile* and 74 volumes of *water* containing 0.93 g per litre of *sodium octyl sulfate* adjusted to pH 3 with 2M *sodium hydroxide*.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{22}N_2O_3$ in the oral solution using the declared content of $C_{14}H_{22}N_2O_3$ in *atenolol BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atenolol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Atenolol Tablets contain Atenolol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of atenolol, $C_{14}H_{22}N_2O_3$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Heat a quantity of the powdered tablets containing 0.1 g of Atenolol with 15 mL of *methanol* to 50°, shake for 5 minutes, filter (Whatman No. 42 paper is suitable) and evaporate the filtrate to dryness on a water bath. Warm the residue with 10 mL of 0.1M *hydrochloric acid*, shake and filter. Add to the filtrate sufficient 1M *sodium hydroxide* to make it alkaline, extract with 10 mL of *chloroform*, dry by shaking with *anhydrous sodium sulfate*, filter, evaporate the filtrate to dryness on a water bath and dry the residue at 105° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of atenolol *(RS 015)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 25 mg of Atenolol with 25 mL of the mobile phase, mix with the aid of ultrasound for 20 minutes, filter (Whatman GF/C filter paper is suitable) and use the filtrate.
(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.
(3) Dissolve 10 mg of *atenolol impurity standard BPCRS* in 0.1 mL of *dimethyl sulfoxide*, with the aid of gentle heat, and dilute to 20 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Luna-C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of impurity G.

MOBILE PHASE

20 volumes of *tetrahydrofuran*, 180 volumes of *methanol* and 800 volumes of 0.025M *potassium dihydrogen orthophosphate*. Dissolve 0.8 g of *sodium octanesulfonate* and 0.4 g of *tetrabutylammonium hydrogen sulfate* to 1 litre of this solution and adjust the pH to 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles that of the reference chromatogram provided with *atenolol impurity standard BPCRS* in that the peak due to impurity E precedes, and is separated from, that due to impurity F, which is normally a doublet. If necessary adjust the concentration of sodium octanesulfonate in the mobile phase; increasing the concentration increases the retention time of impurity F.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity G is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to either impurity E or impurity F is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.25%).

ASSAY

Powder 20 tablets. Transfer the powder to a 500 mL flask using 300 mL of *methanol*, heat the resulting suspension to 60° and shake for 15 minutes. Cool, dilute to 500 mL with *methanol*, filter through a fine glass micro-fibre filter paper (Whatman GF/C is suitable) and dilute a suitable volume of the filtrate with sufficient *methanol* to produce a solution containing 0.01% w/v of Atenolol. Measure the *absorbance* of the resulting solution at the maximum at 275 nm, Appendix II B. Calculate the content of $C_{14}H_{22}N_2O_3$ taking 53.7 as the value of A(1%, 1 cm) at the maximum at 275 nm.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

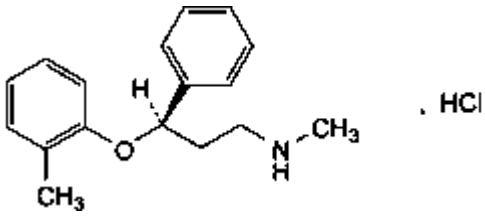
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atomoxetine Hydrochloride

General Notices

(Ph. Eur. monograph 2640)



$C_{17}H_{22}ClNO$ 291.8 *82248-59-7*

Action and use

Noradrenaline reuptake inhibitor; treatment of attention deficit hyperactivity disorder (ADHD).

Ph Eur

DEFINITION

(3*R*)-*N*-Methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, soluble in anhydrous ethanol, practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *atomoxetine hydrochloride CRS*.

www.webofpharma.com

https://thuocngocanh.com/

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

B. Isomeric purity (see Tests).

C. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Isomeric purity

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 35.0 mg of the substance to be examined in 2.5 mL of *anhydrous ethanol R*, sonicate until dissolution is complete and dilute to 10.0 mL with *heptane R*.

Reference solution (a) Dissolve 3.5 mg of *atomoxetine impurity B CRS* and 1 mg of *atomoxetine impurity D CRS* in 5 mL of *anhydrous ethanol R*, sonicate until dissolution is complete and dilute to 20.0 mL with *heptane R*.

Reference solution (b) Dissolve 35.0 mg of the substance to be examined in 2.5 mL of *anhydrous ethanol R*. Add 1.0 mL of reference solution (a) and dilute to 10.0 mL with *heptane R*.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with *heptane R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (5 µm).

Mobile phase Mix 1.5 mL of *diethylamine R*, 2.0 mL of *trifluoroacetic acid R* and 150.0 mL of *2-propanol R* and dilute to 1000 mL with *heptane R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 273 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time 1.3 times the retention time of atomoxetine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and D.

Relative retention With reference to atomoxetine (retention time = about 12 min): impurity B = about 0.5; impurity D = about 0.6.

System suitability Reference solution (b):

— *resolution*: minimum 1.8 between the peaks due to impurities B and D.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity B*: maximum 0.5 per cent;

— *impurity D*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *disregard limit*: the area of the peak due to impurity B in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard any peak with a relative retention with reference to atomoxetine of about 0.7 (impurity A).

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 5.9 g of *sodium octanesulfonate monohydrate R* in 1000 mL of a 2.9 g/L solution of *phosphoric acid R* previously adjusted to pH 2.5 with a 280 g/L solution of *potassium hydroxide R*.

Test solution (a) Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 7.5 mg of *3-(methylamino)-1-phenylpropan-1-ol R* (impurity H) and 5 mg of *mandelic acid R* (impurity E) in test solution (b) and dilute to 50 mL with test solution (b).

Reference solution (c) Dissolve 5 mg of *atomoxetine for impurity A identification CRS* in the mobile phase and dilute to 20 mL with the mobile phase.

Reference solution (d) Dissolve 25.0 mg of *atomoxetine hydrochloride CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase *propanol R*, solution A (27:73 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time 2.5 times the retention time of atomoxetine.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities E and H; use the chromatogram supplied with *atomoxetine for impurity A identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to atomoxetine (retention time = about 10 min): impurity E = about 0.2; impurity H = about 0.3; impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurities E and H.

Calculation of percentage contents:

— for each impurity, use the concentration of atomoxetine hydrochloride in reference solution (a).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{17}H_{22}ClNO$ taking into account the assigned content of *atomoxetine hydrochloride CRS*.

IMPURITIES

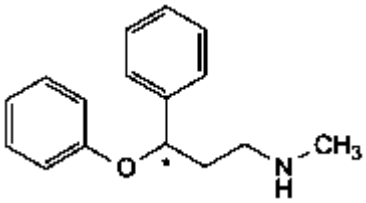
Specified impurities *A, B, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

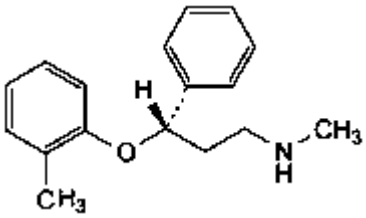
www.webofpharma.com

https://thuocngocanh.com/

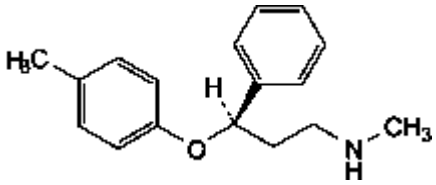
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, E, F, G, H.



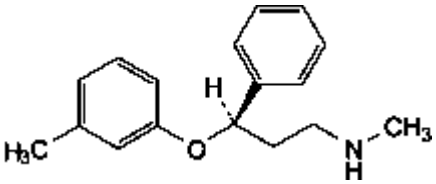
A. *N*-methyl-3-phenoxy-3-phenylpropan-1-amine,



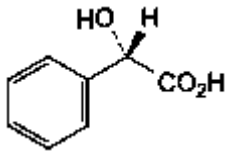
B. (3*S*)-*N*-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine,



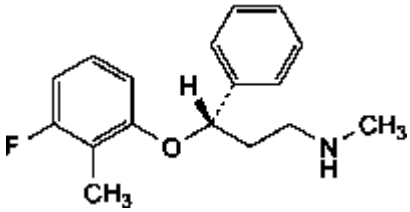
C. (3*R*)-*N*-methyl-3-(4-methylphenoxy)-3-phenylpropan-1-amine,



D. (3*R*)-*N*-methyl-3-(3-methylphenoxy)-3-phenylpropan-1-amine,



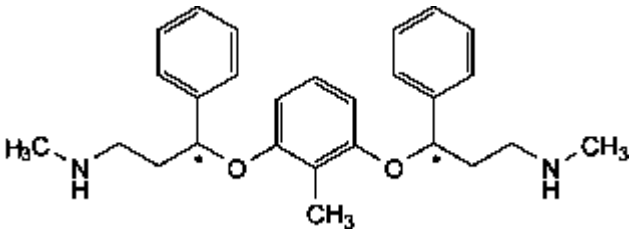
E. (2*S*)-2-hydroxy-2-phenylacetic acid (L-mandelic acid),



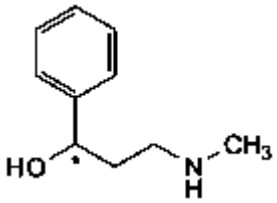
www.webofpharma.com

https://thuocngocanh.com/

F. (3*S*)-3-(3-fluoro-2-methylphenoxy)-*N*-methyl-3-phenylpropan-1-amine,



G. 3,3′-[(2-methylbenzene-1,3-diyl)bis(oxy)]bis(*N*-methyl-3-phenylpropan-1-amine),



H. 3-(methylamino)-1-phenylpropan-1-ol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

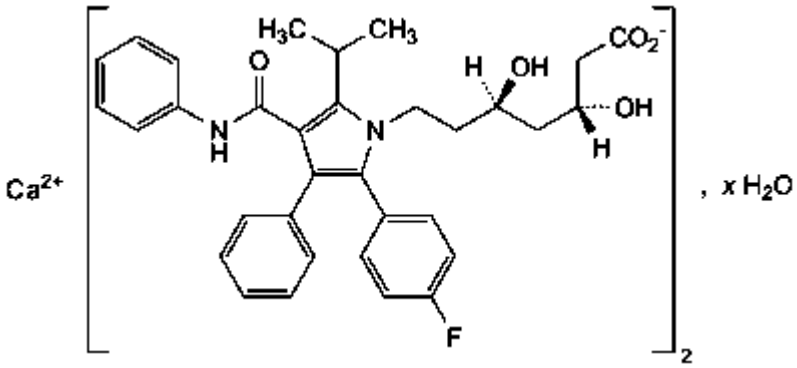
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Atorvastatin Calcium

General Notices

Atorvastatin Calcium Trihydrate

(Ph. Eur. monograph 2191)



$C_{66}H_{68}CaF_2N_4O_{10},xH_2O$ 1155 (anhydrous substance)

Anhydrous atorvastatin calcium *134523-03-8*

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

Preparation

Atorvastatin Tablets

Ph Eur

DEFINITION

Calcium bis[(3*R*,5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate].

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

It may be anhydrous or contain a variable quantity of water.

CHARACTERS

https://thuocngocanh.com/

Appearance

White or almost white to yellowish, amorphous or crystalline powder, not hygroscopic to hygroscopic.

Solubility

Practically insoluble in water, very slightly soluble to very soluble in ethanol (96 per cent), freely soluble to very soluble in methanol, practically insoluble to freely soluble in methylene chloride, freely soluble in dimethyl sulfoxide.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison atorvastatin calcium CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

B. Enantiomeric purity (see Tests).

C. Place 0.5 g of the substance to be examined in a platinum crucible and moisten with 5 mL of sulfuric acid R. Heat gently at as low a temperature as practicable until the sample is thoroughly charred. Continue heating gently until white fumes are no longer evolved and ignite at 600 ± 50 °C until the residue is completely incinerated. Allow the crucible to cool. Suspend the residue in 10 mL of water R and sonicate for 5 min. The residue does not dissolve. Centrifuge the suspension and filter. The residue gives reaction (b) of calcium (2.3.1). Filter after the addition of acetic acid R to remove undissolved particles.

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29). *Store the solutions protected from light in amber flasks*.

Solvent mixture anhydrous ethanol R, heptane R (50:50 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in methanol R using sonication and dilute to 5.0 mL with the same solvent. Dilute 3.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 3.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of atorvastatin impurity mixture CRS (impurities E and H) in 1 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 1 mL of *formic acid R* and 40 mL of *anhydrous ethanol R* and dilute to 1000 mL with *heptane R*.

Flow rate 1.8 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 10 °C.

Injection 5 µL.

Run time 1.2 times the retention time of atorvastatin.

Identification of impurities Use the chromatogram supplied with *atorvastatin impurity mixture CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities E and H.

Relative retention With reference to atorvastatin (retention time = about 35 min): impurity H = about 0.57; impurity E = about 0.66.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities H and E.

Calculation of percentage content:

— for impurity E, use the concentration of atorvastatin calcium in reference solution (a).

Limit:

— *impurity E*: maximum 0.15 per cent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect them from light*.

Buffer solution Dissolve 0.35 g of *ammonium acetate R* and 2.84 g of *ammonium formate R* in 950 mL of *water for chromatography R*. Adjust to pH 5.0 with a 20 per cent *V/V* solution of *formic acid R* and dilute to 1000 mL with *water for chromatography R*.

Solvent mixture *tetrahydrofuran R*, buffer solution, *acetonitrile R* (5:35:60 *V/V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture using sonication and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 25.0 mg of *atorvastatin calcium CRS* in the solvent mixture using sonication and dilute to 50.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Dissolve 2 mg of *atorvastatin for peak identification A CRS* (containing impurities A, B, F and G) in 4 mL of the solvent mixture using sonication.

Reference solution (d) Dissolve 2 mg of *atorvastatin for peak identification B CRS* (containing impurities D1 and D2) in 4 mL of the solvent mixture using sonication.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped propoxybenzene silica gel for chromatography R* (4 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, buffer solution (33:67 *V/V*);

— *mobile phase B*: *acetonitrile R*;

— *mobile phase C*: *tetrahydrofuran for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 15	91	0 → 6	9 → 3
15 - 20	91 → 82	6 → 16	3 → 2
20 - 25	82	16	2
25 - 50	82 → 32	16 → 66	2
50 - 55	32	66	2

Flow rate 1.1 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 4 °C.

Injection 15 µL of the test solution and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram supplied with *atorvastatin for peak identification A CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, F and G; use the chromatogram supplied with *atorvastatin for peak identification B CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities D1 and D2.

Relative retention With reference to atorvastatin (retention time = about 19 min): impurity F = about 0.6; impurity A = about 0.87; impurity B = about 0.94; impurity G = about 1.3; impurity D2 = about 2.0; impurity D1 = about 2.2.

www.webofpharma.com

https://thietbiuocngocanh.com/

System suitability:

— *signal-to-noise ratio*: minimum 28 for the principal peak in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to atorvastatin in the chromatogram obtained with reference solution (c).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D2 = 1.4; impurity F = 1.4; impurity G = 1.3;

— for each impurity, use the concentration of atorvastatin calcium in reference solution (a).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *impurity D*: maximum 0.15 per cent for the sum of the areas of the 2 peaks;

— *impurities F, G*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Sodium (*2.4.20*)

Maximum 0.4 per cent (anhydrous substance).

Water (*2.5.12*)

Maximum 6.0 per cent, determined on 0.130 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{66}H_{68}CaF_2N_4O_{10}$ taking into account the assigned content of *atorvastatin calcium CRS*.

STORAGE

In an airtight container.

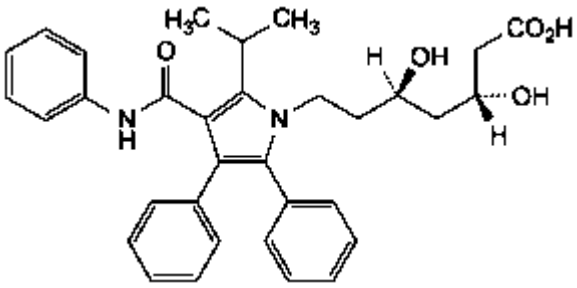
www.webofpharma.com

https://thuocngocanh.com/

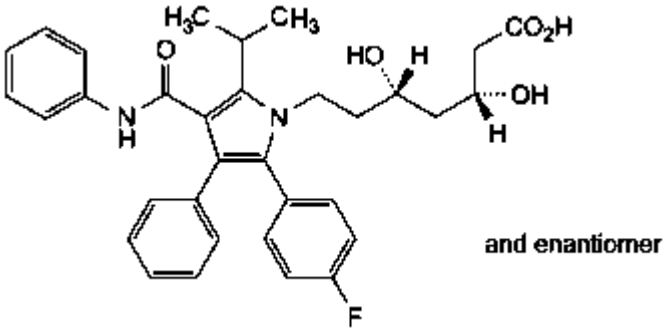
IMPURITIES

Specified impurities *A, D, E, F, G.*

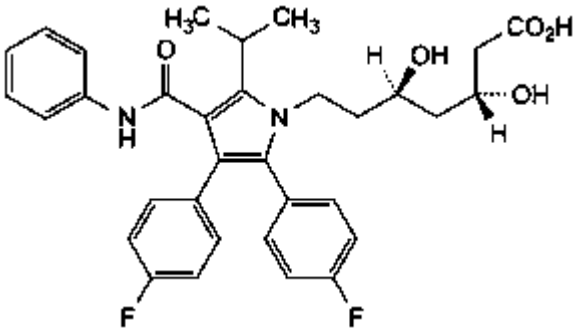
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, H, I, J, K, M, N, O, P, Q.*



A. (3*R*,5*R*)-7-[2,3-diphenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid (defluoroatorvastatin),



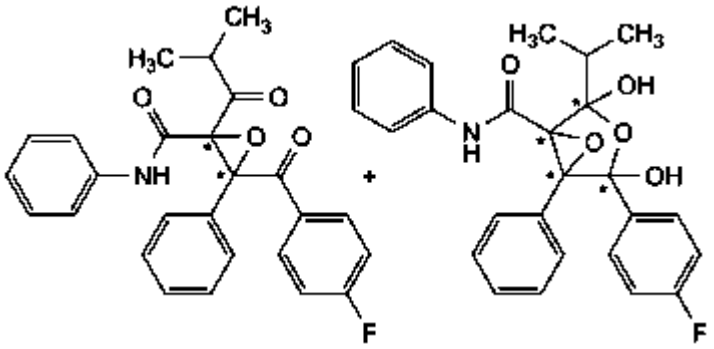
B. (3*RS*,5*SR*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid,



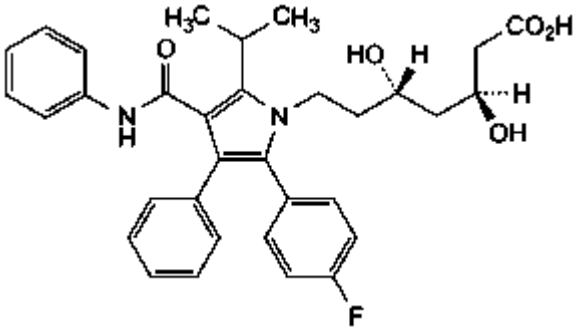
C. (3*R*,5*R*)-7-[2,3-bis(4-fluorophenyl)-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid (fluoroatorvastatin),

www.webofpharma.com

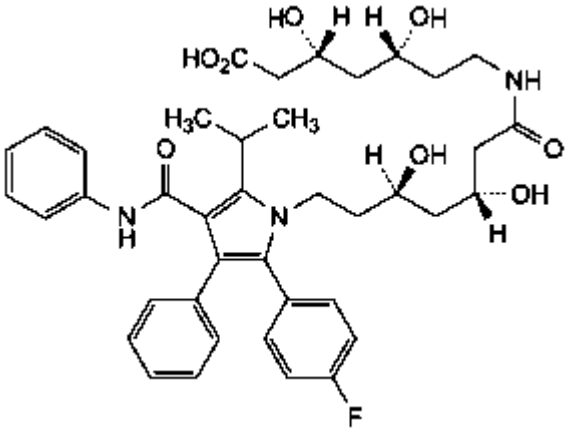
https://thuocngocanh.com/



D. mixture of (2Ξ,3Ξ)-3-(4-fluorobenzoyl)-2-(2-methylpropanoyl)-*N*,3-diphenyloxirane-2-carboxamide (D1) and (1Ξ,2Ξ,4Ξ,5Ξ)-4-(4-fluorophenyl)-2,4-dihydroxy-*N*,5-diphenyl-2-(propan-2-yl)-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide (D2),



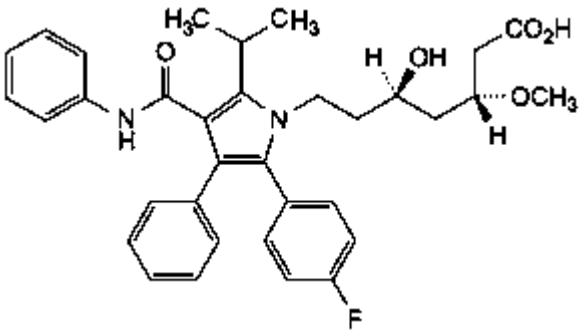
E. (3*S*,5*S*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid (*ent*-atorvastatin),



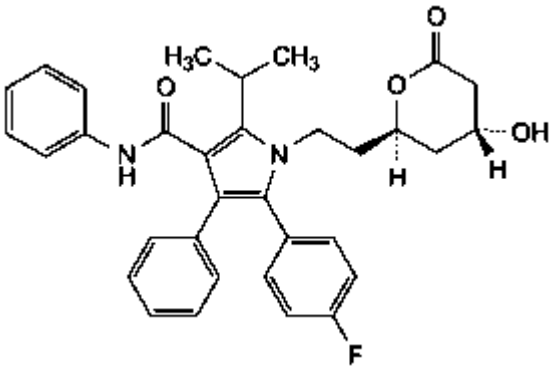
F. (3*R*,5*R*)-7-[(3*R*,5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanamido]-3,5-dihydroxyheptanoic acid,

www.webofpharma.com

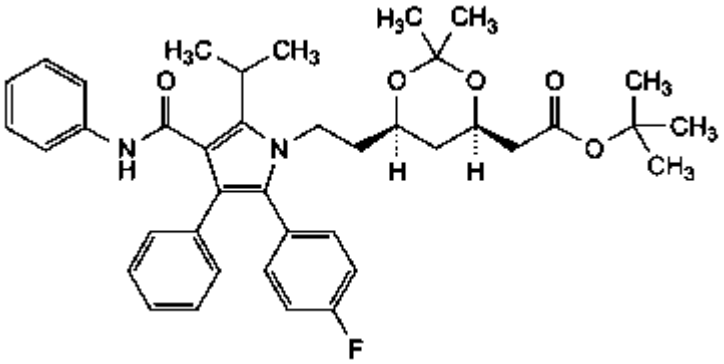
https://thuocngocanh.com/



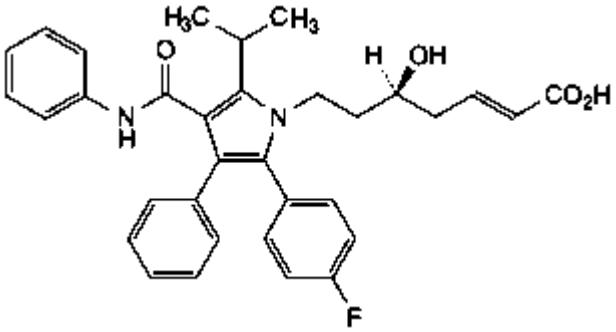
G. (3*R*,5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-5-hydroxy-3-methoxyheptanoic acid (3-*O*-methylatorvastatin),



H. (4*R*,6*R*)-6-[2-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]ethyl]-4-hydroxyoxan-2-one,



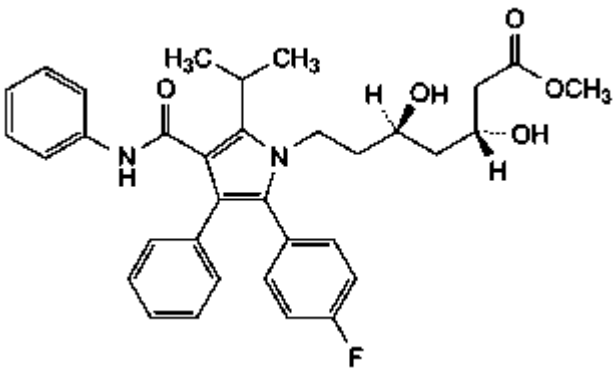
I. *tert*-butyl [(4*R*,6*R*)-6-[2-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]acetate,



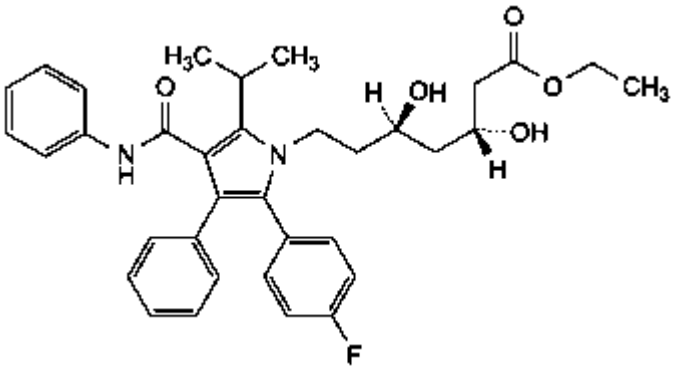
www.webofpharma.com

https://thuocngocanh.com/

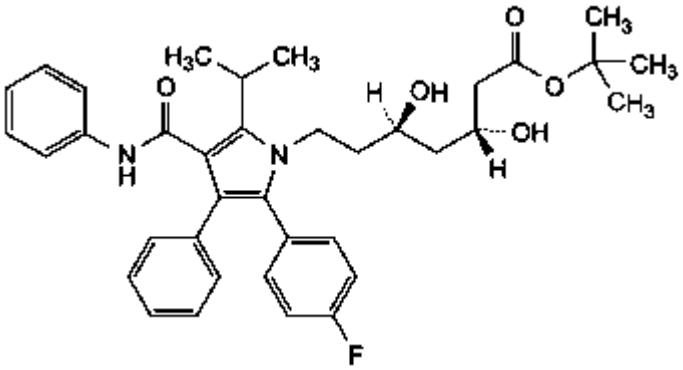
J. (2*E*,5*S*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-5-hydroxyhept-2-enoic acid,



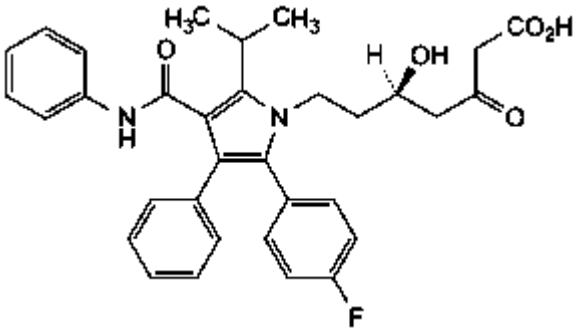
K. methyl (3*R*,5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate,



M. ethyl (3*R*,5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate,



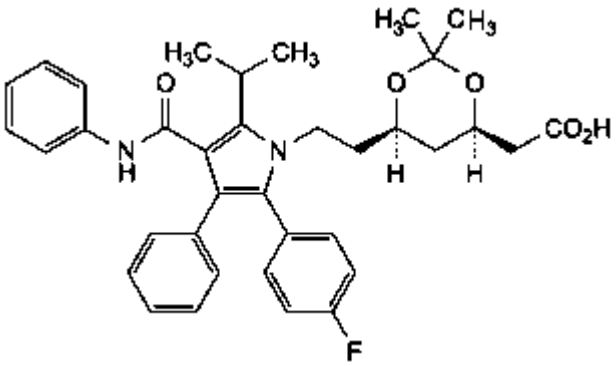
N. *tert*-butyl (3*R*,5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate,



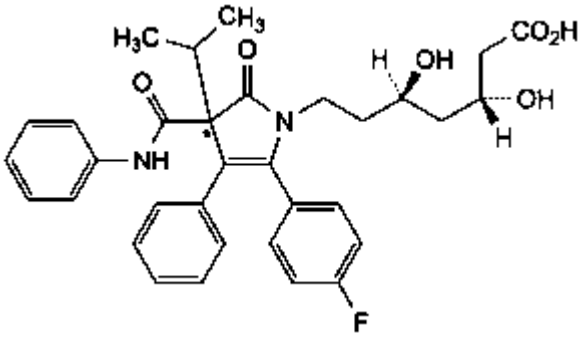
www.webofpharma.com

https://thuocngocanh.com/

O. (5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxoheptanoic acid,



P. [(4*R*,6*R*)-6-[2-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1*H*-pyrrol-1-yl]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]acetic acid,



Q. (3*R*,5*R*)-7-[5-(4-fluorophenyl)-2-oxo-4-phenyl-3-(phenylcarbamoyl)-3-(propan-2-yl)-2,3-dihydro-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atorvastatin Tablets

General Notices

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

DEFINITION

Atorvastatin Tablets contain Atorvastatin Calcium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of atorvastatin, $C_{33}H_{35}FN_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of a solution containing 0.05M *potassium dihydrogen orthophosphate* adjusted to pH 6.8 using 6M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution expected to contain the equivalent of 0.0011% w/v of atorvastatin, at the maximum

www.webofpharma.com

https://thuocngocanh.com/

at 244 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0011% w/v solution of *atorvastatin calcium BPCRS* in the dissolution medium, using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of atorvastatin, $C_{33}H_{35}FN_2O_5$, in the medium from the absorbances obtained and using the declared content of $2(C_{33}H_{34}FN_2O_5),Ca$ in *atorvastatin calcium BPCRS*.

Each mg of $2(C_{33}H_{34}FN_2O_5),Ca$ is equivalent to 0.9671 mg of $C_{33}H_{35}FN_2O_5$.

LIMITS

The amount of atorvastatin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A Equal volumes of *acetonitrile* and 0.05M *citric acid*, previously adjusted to pH 7.4 with *dilute ammonia R1*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of atorvastatin with 80 mL of solution A, dilute to 100 mL and filter (a 0.45-µm PTFE filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.1% w/v of *atorvastatin for peak identification A EPCRS*.
(4) 0.1% w/v of *atorvastatin impurity BPCRS*.
(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use the flow rates described below.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 244 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Solution B 75 volumes of *stabiliser-free tetrahydrofuran* and 925 volumes of *acetonitrile*.

Solution C 0.05M *ammonium dihydrogen orthophosphate*, previously adjusted to pH 4.3 with *dilute acetic acid* or *dilute ammonia R1*.

Mobile phase A 42 volumes of solution B and 58 volumes of solution C.

Mobile phase B 20 volumes of solution B, 20 volumes of solution C and 60 volumes of *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Flow rate (mL per minute)	Comment
0-30	100	0	1.8	isocratic
30-45	100→25	0→75	1.8	linear gradient
45-50	25	75	1.5	isocratic
50-55	25→20	75→80	1.5	linear gradient
55-58	20→100	80→0	1.8	linear gradient
58-65	100	0	1.8	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to atorvastatin and impurity B is at least 1.4;

the *signal-to-noise ratio* of the peak due to atorvastatin in the chromatogram obtained with solution (5) is at least 20.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of atorvastatin in solution (2).

For the reporting threshold, use the concentration of atorvastatin in solution (5).

For peak identification, use solutions (3) and (4).

Atorvastatin retention time: about 19 minutes.

Relative retention: impurity A, about 0.85; impurity 1, about 0.9; impurity B, about 0.95; impurity H, about 2.0; impurity 2, about 2.1; impurity 3, about 2.3; impurity 4, about 2.4.

Correction factors: impurity 1, multiply by 1.5; impurities 2 and 3, multiply by 1.9.

LIMITS

— impurities H, 1, 2 and 3: not more than 0.5% of each;

— impurity A: not more than 0.3%;

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 2.0%;

— reporting threshold: 0.1%.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A Equal volumes of *acetonitrile* and 0.05M *citric acid*, previously adjusted to pH 7.4 with *dilute ammonia R1*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of atorvastatin with 80 mL of solution A, dilute to 100 mL and filter (a 0.45-µm PTFE filter is suitable). Dilute the 1 volume of the filtrate to 10 volumes.
(2) 0.01% w/v of *atorvastatin calcium BPCRS*.
(3) 0.01% w/v of *atorvastatin impurity BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Ultremex C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 244 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *stabiliser-free tetrahydrofuran*, 27 volumes of *acetonitrile* and 53 volumes 0.05M *citric acid*, previously adjusted to pH 4.0 using *dilute ammonia R1*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to atorvastatin (retention time about 9 minutes) is impurity H, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to atorvastatin and impurity H is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of atorvastatin, $C_{33}H_{35}FN_2O_5$, in the tablets from the chromatograms obtained and using the declared content of $2(C_{33}H_{34}FN_2O_5),Ca$ in *atorvastatin calcium BPCRS*.

Each mg of $2(C_{33}H_{34}FN_2O_5),Ca$ is equivalent to 0.9671 mg of $C_{33}H_{35}FN_2O_5$.

Supporting information for Assay

Analytical Quality by Design concepts were applied in the development of this Assay, Supplementary Chapter X on the use of Analytical Quality by Design concepts for analytical procedures. The "More resources" tab, available in the BP online monograph, provides additional information on the ranges for sample preparation and chromatographic parameters that were found to be suitable, as well as method performance, to aid user investigations into method suitability.

LABELLING

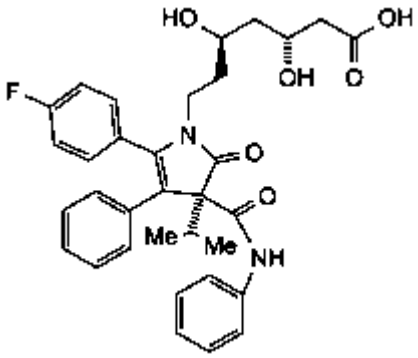
www.webofpharma.com

https://thuocngocanh.com/

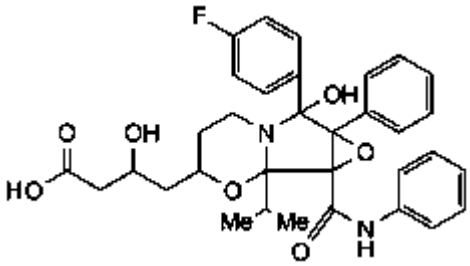
The quantity of active ingredient is stated in terms of the equivalent amount of atorvastatin.

IMPURITIES

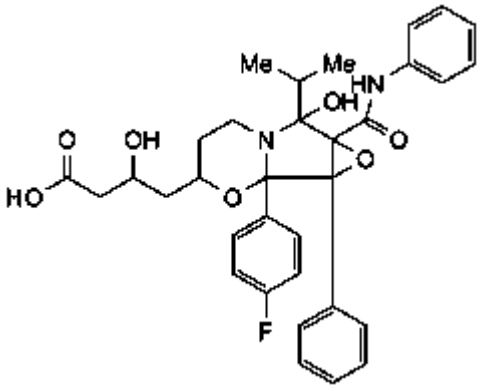
The impurities limited by the requirements of this monograph include impurities A, B, C, D, F and H listed under Atorvastatin Calcium and:



1. (3*R*,5*R*)-{(3*R*)-5-(4-fluorophenyl)-2-oxo-4-phenyl-3-(*N*-phenylcarbamoyl)-3-(propan-2-yl)-2,3-dihydro-1*H*-pyrrol-1-yl}-3,5-dihydroxyheptanoic acid (pyrrolidone analogue)



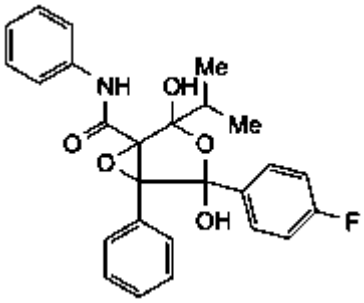
2. 4-[7-(4-fluorophenyl)-7-hydroxy-7a-phenyl-1a-(phenylcarbamoyl)-1b-(propan-2-yl]hexahydro-3*H*-oxireno[3,4]pyrrolo[2,1-*b*][1,3]oxazin-3-yl)-3-hydroxybutanoic acid (epoxy pyrrolooxazin 6-hydroxy analogue)



3. 4-[1b-(4-fluorophenyl)-7-hydroxy-1a-phenyl-7a-(phenylcarbamoyl)-7-(propan-2-yl)hexahydro-3*H*-oxireno[3,4]pyrrolo[2,1-*b*][1,3]oxazin-3-yl]-3-hydroxybutanoic acid (epoxy pyrrolooxazin 7-hydroxy analogue)

www.webofpharma.com

https://thuocngocanh.com/



4. 4-(4-fluorophenyl)-2,4-dihydroxy-2-isopropyl-*N*,5-diphenyl-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide (epoxy THF analogue)

© Crown Copyright 2022

www.webofpharma.com

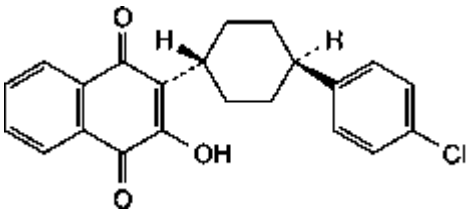
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atovaquone

General Notices

(Ph. Eur. monograph 2192)



$C_{22}H_{19}ClO_3$ 366.8 *95233-18-4*

Action and use

Antiprotozoal (malaria).

Ph Eur

DEFINITION

2-[*trans*-4-(4-Chlorophenyl)cyclohexyl]-3-hydroxynaphthalene-1,4-dione.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *atovaquone CRS*.

If the spectra obtained show differences, dissolve 0.1 g of the substance to be examined and 0.1 g of the reference substance separately in 2.5 mL of a 50 g/L solution of *potassium hydroxide R* in *methanol R*. Filter the solutions and add each filtrate dropwise to a mixture of 0.8 mL of *acetic acid R* and 1.5 mL of *methanol R*, stirring continuously. Filter, wash the residues with *methanol R* and then with *water R*, and dry under vacuum at 55 °C. Record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture *water R*, *acetonitrile R1* (20:80 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of *atovaquone CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.5 mg of *atovaquone for system suitability CRS* (containing impurities B and C) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *phosphoric acid R*, *methanol R2*, *water for chromatography R*, *acetonitrile R1* (0.5:17.5:30:52.5 *V/V/V/V*).

Flow rate 2.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of atovaquone.

Identification of impurities Use the chromatogram supplied with *atovaquone for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to atovaquone (retention time = about 15 min): impurity B = about 0.85; impurity C = about 0.90.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity C and atovaquone;

www.webofpharma.com

https://thuocngocanh.com/

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Calculation of percentage contents:

— for each impurity, use the concentration of atovaquone in reference solution (c).

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurity C*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

Maximum 0.3 per cent, determined on 0.100 g using the evaporation technique:

— *temperature*: 160 °C;

— *heating time*: 3 min;

— *flow rate*: 50 mL/min.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{22}H_{19}ClO_3$ taking into account the assigned content of *atovaquone CRS*.

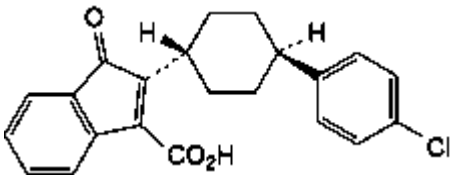
IMPURITIES

Specified impurities *B, C.*

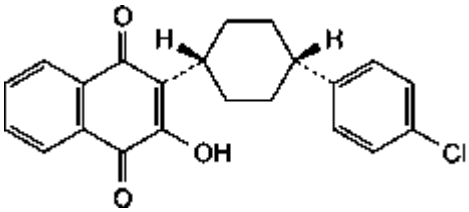
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D.*

www.webofpharma.com

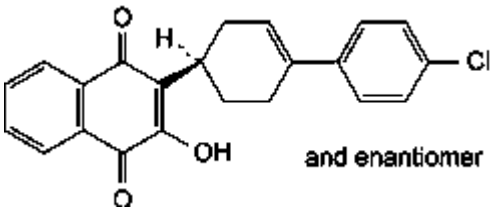
https://thuocngocanh.com/



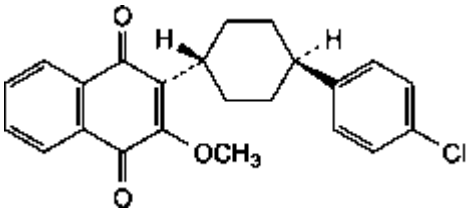
A. 2-[*trans*-4-(4-chlorophenyl)cyclohexyl]-1-oxo-1*H*-indene-3-carboxylic acid,



B. 2-[*cis*-4-(4-chlorophenyl)cyclohexyl]-3-hydroxynaphthalene-1,4-dione,



C. 2-[(1*RS*)-4-(4-chlorophenyl)cyclohex-3-en-1-yl]-3-hydroxynaphthalene-1,4-dione,



D. 2-[*trans*-4-(4-chlorophenyl)cyclohexyl]-3-methoxynaphthalene-1,4-dione.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

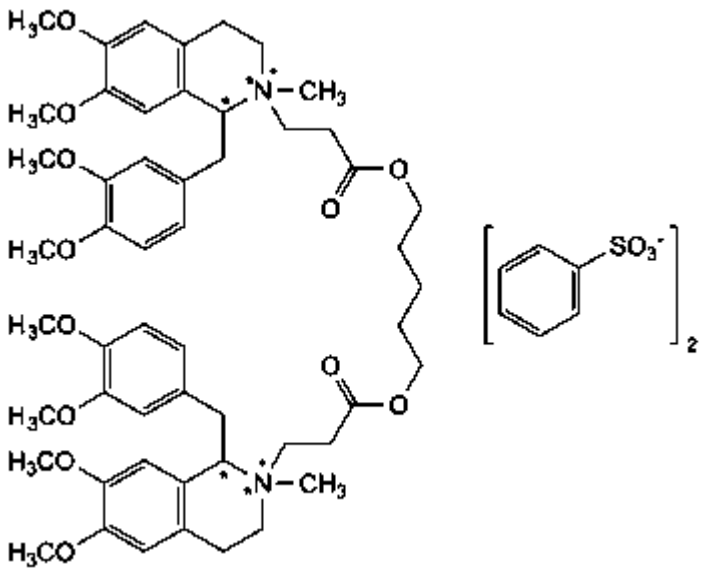
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atracurium Besilate

General Notices

(Ph. Eur. monograph 1970)



$C_{65}H_{82}N_2O_{18}S_2$ 1243 *64228-81-5*

Action and use

Non-depolarizing neuromuscular blocker.

Ph Eur

DEFINITION

Mixture of the *cis-cis*, *cis-trans* and *trans-trans* isomers of 2,2′-[pentane-1,5-diylbis[oxy(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium] dibenzenesulfonate.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl benzenesulfonate esters are genotoxic and are potential impurities in atracurium besilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality

www.webofpharma.com

https://thuocngocanh.com/

of starting materials, process capability and validation. The general method 2.5.41. *Methyl, ethyl and isopropyl benzenesulfonate in active substances* is available to assist manufacturers.

CHARACTERS

Appearance

White or yellowish-white, slightly hygroscopic powder.

Solubility

Soluble in water, very soluble in acetonitrile, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *atracurium besilate CRS*.

B. Examine the chromatograms obtained in the assay.

Results The 3 principal isomeric peaks in the chromatogram obtained with test solution (a) are similar in retention time to those in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 1.00 g in *water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Test solution (b) Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 50.0 mg of *atracurium besilate CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with mobile phase A.

Reference solution (c) Dissolve 20.0 mg of *methyl benzenesulfonate R* in *acetonitrile R* and dilute to 100.0 mL with the same solvent. Dilute 50 µL of the solution to 100.0 mL with mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dissolve 2.0 mg of *atracurium for peak identification CRS* (containing impurities A1, A2, B, C1, C2, D1, D2, E, G and K) in 2.0 mL of mobile phase A.

Reference solution (e) Dissolve 2.0 mg of *atracurium for impurity F identification CRS* in 2.0 mL of mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 5 volumes of *methanol R*, 20 volumes of *acetonitrile R* and 75 volumes of a 10.2 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.1 with *phosphoric acid R*;

— *mobile phase B*: mix 20 volumes of *acetonitrile R*, 30 volumes of *methanol R* and 50 volumes of a 10.2 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.1 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 15	80 → 40	20 → 60
15 - 25	40	60
25 - 30	40 → 0	60 → 100
30 - 45	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b), (d) and (e).

Identification of impurities Use the chromatogram obtained with reference solution (d) and the chromatogram supplied with *atracurium for peak identification CRS* to identify the peaks due to impurities A1, A2, B, C1, C2, D1, D2, E, G and K; use the chromatogram obtained with reference solution (e) and the chromatogram supplied with *atracurium for impurity F identification CRS* to identify the peak due to impurity F.

Relative retention With reference to the atracurium *cis-cis* isomer (retention time = about 30 min): impurity E = about 0.2; impurity F = about 0.25; impurity G = about 0.3; impurity D1 = about 0.45; impurity D2 = about 0.5; atracurium *trans-trans* isomer = about 0.8; atracurium *cis-trans* isomer = about 0.9; impurity A1 = about 1.04; impurity I1 = about 1.07; impurity H1 = about 1.07 (shoulder on the front of peak A2); impurity A2 (major isomer) = about 1.08; impurity K1 = about 1.09 (shoulder on

www.webofpharma.com

https://thuvienthuocngocanh.com/

the tail of peak A2); impurity I2 (major isomer) = about 1.12; impurity H2 (major isomer) = about 1.12; impurity K2 (major isomer) = about 1.12; impurity B = about 1.15; impurity C1 = about 1.2; impurity C2 (major isomer) = about 1.3.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to the atracurium *trans-trans* isomer and the atracurium *cis-trans* isomer, and minimum 1.5 between the peaks due to the atracurium *cis-trans* isomer and the atracurium *cis-cis* isomer in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to impurity A1 and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the atracurium *cis-cis* isomer in the chromatogram obtained with reference solution (d).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 0.5;

— *impurity E*: not more than 1.5 times the sum of the areas of the peaks due to the atracurium *cis-cis*, *trans-trans* and *cis-trans* isomers in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *impurities A, D*: for each impurity, for the sum of the areas of the 2 isomer peaks, not more than 1.5 times the sum of the areas of the peaks due to the atracurium *cis-cis*, *trans-trans* and *cis-trans* isomers in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *impurity C*: for the sum of the areas of the 2 isomer peaks, not more than the sum of the areas of the peaks due to the atracurium *cis-cis*, *trans-trans* and *cis-trans* isomers in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurities F, G*: for each impurity, not more than the sum of the areas of the peaks due to the atracurium *cis-cis*, *trans-trans* and *cis-trans* isomers in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurities H, I, K*: for the sum of the areas of the isomer peaks of these impurities, not more than the sum of the areas of the peaks due to the atracurium *cis-cis*, *trans-trans* and *cis-trans* isomers in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the sum of the areas of the peaks due to the atracurium *cis-cis*, *trans-trans* and *cis-trans* isomers in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3.5 times the sum of the areas of the peaks due to the atracurium *cis-cis*, *trans-trans* and *cis-trans* isomers in the chromatogram obtained with reference solution (b) (3.5 per cent);

— *disregard limit*: 0.05 times the sum of the areas of the peaks due to the atracurium *cis-cis*, *trans-trans* and *cis-trans* isomers in the chromatogram obtained with reference solution (b) (0.05 per cent).

Impurity J

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 15	80 → 75	20 → 25
15 - 25	75	25
25 - 30	75 → 55	25 → 45
30 - 38	55 → 0	45 → 100
38 - 45	0	100

Detection Spectrophotometer at 217 nm.

Injection 100 µL of test solution (b) and reference solution (c).

Retention time Impurity J = about 25 min; atracurium *trans-trans* isomer = about 38 min.

Limit:

— *impurity J*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (10 ppm).

Isomer composition

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification. Use the normalisation procedure.

Injection Test solution (a).

Limits:

— *atracurium cis-cis isomer*: 55.0 per cent to 60.0 per cent,

— *atracurium cis-trans isomer*: 34.5 per cent to 38.5 per cent,

— *atracurium trans-trans isomer*: 5.0 per cent to 6.5 per cent.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

www.webofpharma.com

https://thuocngocanh.com/

Injection Test solution (a) and reference solution (a).

Calculate the percentage content of $C_{65}H_{82}N_2O_{18}S_2$ from the sum of the areas of the peaks due to the 3 isomers.

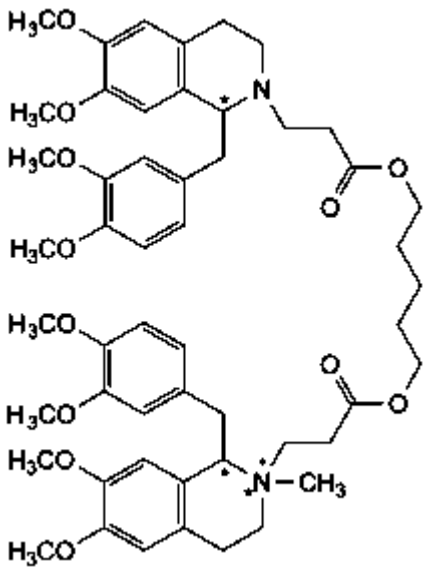
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A, C, D, E, F, G, H, I, J, K.*

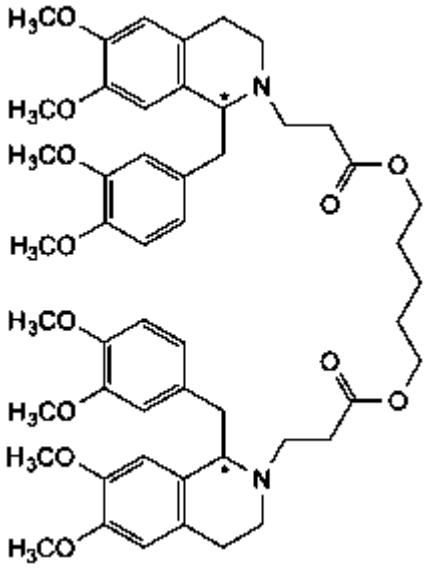
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B.*



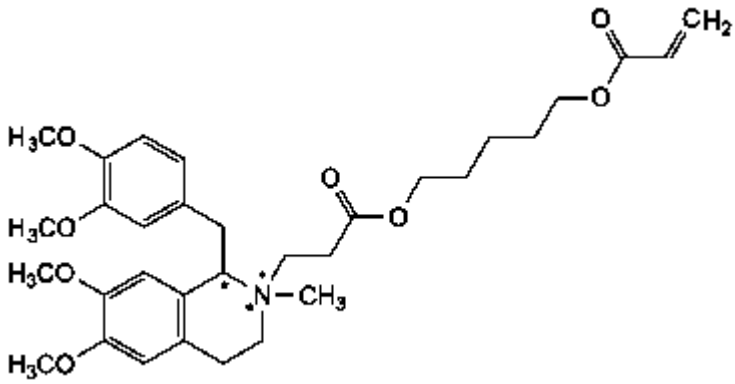
A. 1-(3,4-dimethoxybenzyl)-2-[13-[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]-3,11-dioxo-4,10-dioxatridecyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium (A1 = *trans* isomer, A2 = *cis* isomer),

www.webofpharma.com

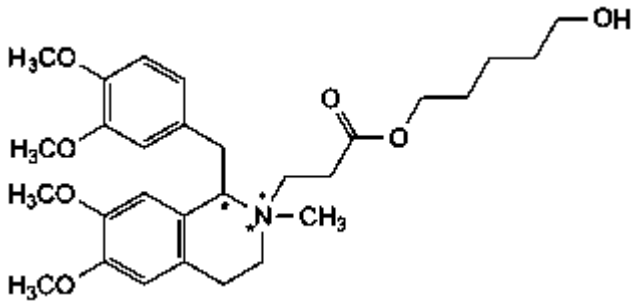
https://thuocngocanh.com/



B. pentane-1,5-diyl bis[3-[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]propanoate],



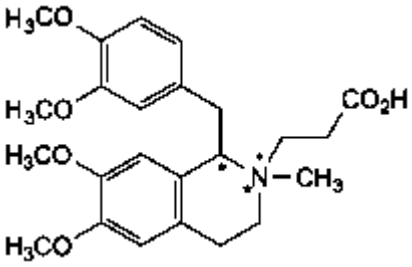
C. 1-(3,4-dimethoxybenzyl)-2-(3,11-dioxo-4,10-dioxatridec-12-enyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium (C1 = *trans* isomer, C2 = *cis* isomer),



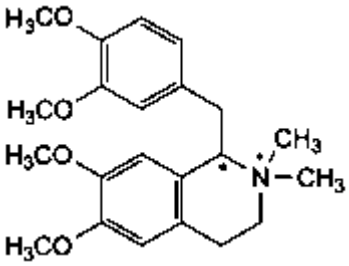
D. 1-(3,4-dimethoxybenzyl)-2-[3-[(5-hydroxypentyl)oxy]-3-oxopropyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium (D1 = *trans* isomer, D2 = *cis* isomer),

www.webofpharma.com

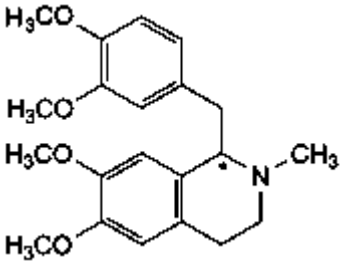
https://thuocngocanh.com/



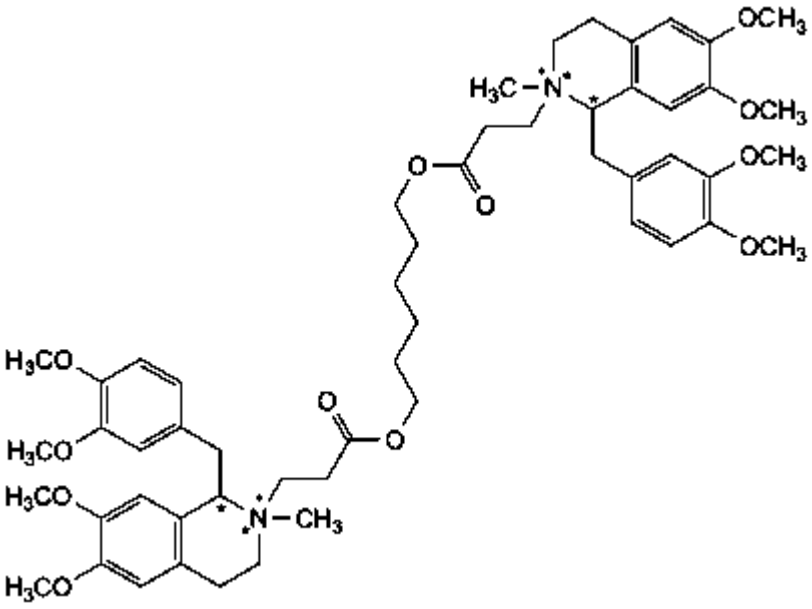
E. 2-(2-carboxyethyl)-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium,



F. 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium,



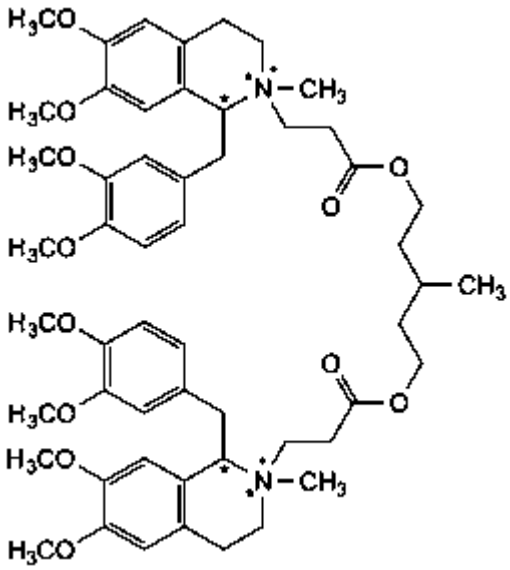
G. 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline,



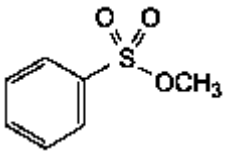
H. 2,2′-[hexane-1,6-diylbis[oxy(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium] (H1 = *cis-trans* isomer, H2 = *cis-cis* isomer),

www.webofpharma.com

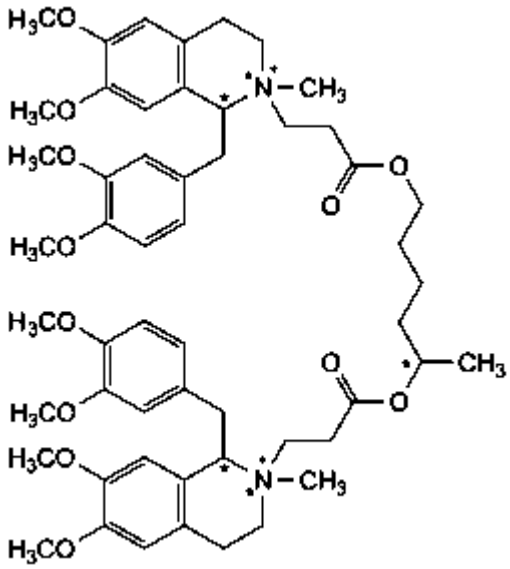
https://thuocngocanh.com/



I. 2,2′-[(3-methylpentane-1,5-diyl)bis[oxy(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium] (I1 = *cis-trans* isomer, I2 = *cis-cis* isomer),



J. methyl benzenesulfonate,



K. 2,2′-[hexane-1,5-diylbis[oxy(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium].

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

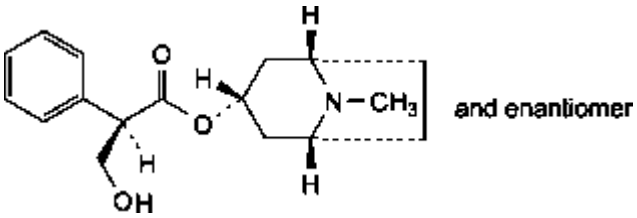
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atropine

General Notices

(Ph. Eur. monograph 2056)



$C_{17}H_{23}NO_3$ 289.4 *51-55-8*

Action and use

Anticholinergic.

Ph Eur

DEFINITION

(1*R*,3*R*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 115 °C to 119 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thietbiuocngocanh.com/

Comparison *atropine CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *atropine CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *water R*, *acetone R* (3:7:90 *V/V/V*).

Application 10 µL.

Development Over half of the plate.

Drying At 100-105 °C for 15 min.

Detection After cooling, spray with *dilute potassium iodobismuthate solution R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Place about 3 mg in a porcelain crucible and add 0.2 mL of *fuming nitric acid R*. Evaporate to dryness on a water-bath. Dissolve the residue in 0.5 mL of a 30 g/L solution of *potassium hydroxide R* in *methanol R*; a violet colour develops.

E. Optical rotation (see Tests).

TESTS

Optical rotation (*2.2.7*)

-0.70° to + 0.05° (measured in a 2 dm tube).

Dissolve 1.25 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 24 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of *atropine impurity B CRS* in the test solution and dilute to 20 mL with the test solution. Dilute 5 mL of this solution to 25 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of *atropine for peak identification CRS* (containing impurities A, D, E, F, G and H) in 1 mL of mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dissolve 5 mg of *tropic acid R* (impurity C) in mobile phase A and dilute to 10 mL with mobile phase A. Dilute 1 mL of the solution to 100 mL with mobile phase A. Dilute 1 mL of this solution to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: dissolve 3.5 g of *sodium dodecyl sulfate R* in 606 mL of a 7.0 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.3 with a 5.8 g/L solution of *phosphoric acid R*, and mix with 320 mL of *acetonitrile R1*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	95	5
2 - 20	95 → 70	5 → 30

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *atropine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, D, E, F, G and H; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to atropine (retention time = about 11 min): impurity C = about 0.2; impurity E = about 0.67; impurity D = about 0.73; impurity F = about 0.8; impurity B = about 0.89; impurity H = about 0.93; impurity G = about 1.1; impurity A = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity B and atropine.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity C = 0.6;

— *impurities E, H*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *impurities A, B, C, D, F, G*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.2 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

ASSAY

Dissolve 0.250 g in 40 mL of *anhydrous acetic acid R*, heating if necessary, and allow to cool. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

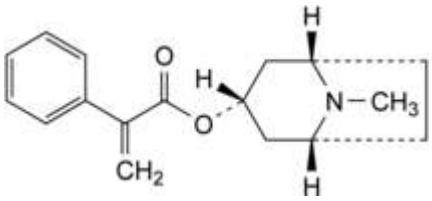
1 mL of *0.1 M perchloric acid* is equivalent to 28.94 mg of $C_{17}H_{23}NO_3$.

STORAGE

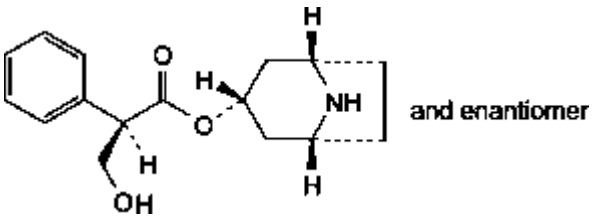
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H.*



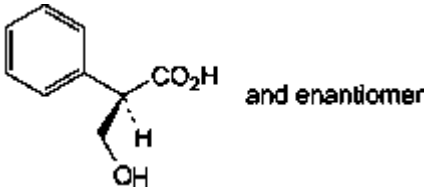
A. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 2-phenylpropenoate (apoatropine),



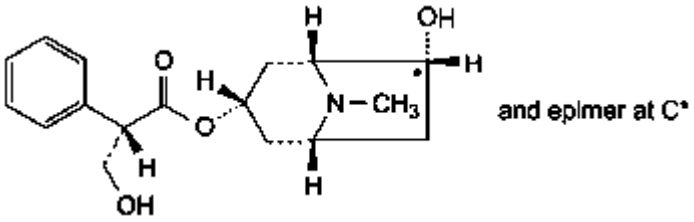
B. (1*R*,3*r*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate (noratropine),

www.webofpharma.com

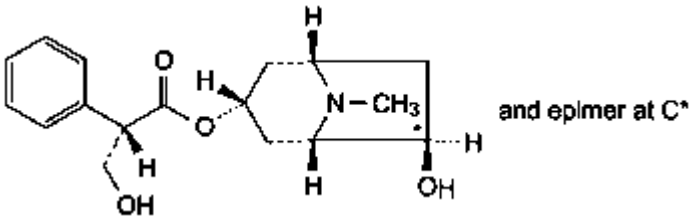
https://thuocngocanh.com/



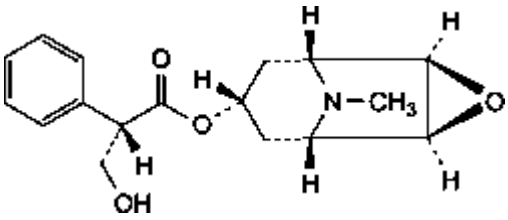
C. (2*RS*)-3-hydroxy-2-phenylpropanoic acid (tropic acid),



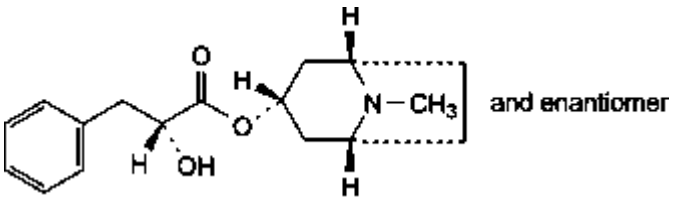
D. (1*R*,3*S*,5*R*,6*RS*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate (6-hydroxyhyoscyamine),



E. (1*S*,3*R*,5*S*,6*RS*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate (7-hydroxyhyoscyamine),



F. (1*R*,2*R*,4*S*,5*S*,7*s*)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate (hyoscine),



G. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-2-hydroxy-3-phenylpropanoate (littorine),

H. unknown structure.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atropine Eye Drops

General Notices

Action and use

Anticholinergic.

DEFINITION

Atropine Eye Drops are a sterile solution of Atropine Sulfate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of atropine sulfate, $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Comply with test A for Identification described under Atropine Injection, using for the preparation of solution (1) a volume of the eye drops containing 5 mg of Atropine Sulfate.

B. In the Assay, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the peak due to atropine sulfate in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For eye drops containing less than 0.1% w/v of Atropine Sulfate.

(1) Use the eye drops being examined.

(2) 0.05% w/v of *atropine sulfate BPCRS* and 0.05% w/v of *homatropine hydrobromide BPCRS* in the mobile phase.

For eye drops containing 0.1% w/v of Atropine Sulfate or more.

(1) Dilute the eye drops to contain 0.1% w/v of Atropine Sulfate with *water*.

(2) 0.1% w/v of *atropine sulfate BPCRS* and 0.1% w/v of *homatropine hydrobromide BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

www.webofpharma.com

https://thuvienthuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 257 nm.

(f) For eye drops containing less than 0.1% w/v of Atropine Sulfate inject 100 µL of each solution. For eye drops containing 0.1% w/v of Atropine Sulfate or more inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium acetate* and 0.005M *dioctyl sodium sulfosuccinate* in *methanol (60%)* adjusted to pH 5.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to atropine sulfate and homatropine hydrobromide is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in the eye drops using the declared content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in *atropine sulfate BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atropine Eye Ointment

General Notices

Action and use

Anticholinergic.

DEFINITION

Atropine Eye Ointment is a sterile preparation containing Atropine Sulfate in a suitable basis.

The eye ointment complies with the requirements stated under Eye Preparations and with the following requirements.

Content of atropine sulfate, $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. Complies with test A for Identification described under Atropine Injection but preparing solution (1) in the following manner. Dissolve a quantity of the ointment containing 10 mg of Atropine Sulfate as completely as possible in 10 mL of *petroleum spirit (boiling range, 40° to 60°)* and extract with two 10 mL quantities of 0.05M *sulfuric acid*, washing each acid solution with the same 5 mL of *petroleum spirit (boiling range, 40° to 60°)*. Mix the acid solutions, make alkaline with 5M *ammonia* and extract with two 15 mL quantities of *chloroform*. Evaporate the chloroform and dissolve the residue in 2 mL of *ethanol (96%)*.

B. In the Assay, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the peak due to atropine sulfate in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the eye ointment containing 10 mg of Atropine Sulfate in 10 mL of *ether* and extract with two 10 mL quantities of 0.01M *hydrochloric acid*. Use the combined extracts.

(2) 0.05% w/v of *atropine sulfate BPCRS* and 0.05% w/v of *homatropine hydrobromide BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 257 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

0.01M *sodium acetate* and 0.005M *dioctyl sodium sulfosuccinate* in *methanol* *(60%)* adjusted to pH 5.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to atropine sulfate and homatropine hydrobromide is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in the eye ointment using the declared content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in *atropine sulfate* *BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atropine Injection

General Notices

Action and use

Anticholinergic.

DEFINITION

Atropine Injection is a sterile solution of Atropine Sulfate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of atropine sulfate, $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Evaporate a volume of the injection containing 5 mg of Atropine Sulfate to dryness on a water bath, triturate the residue with 1 mL of *ethanol (96%)*, allow to stand and use the supernatant liquid.

(2) 0.5% w/v of *atropine sulfate BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat it at 105° for 20 minutes, allow to cool and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

10 volumes of *diethylamine*, 40 volumes of *acetone* and 50 volumes of *chloroform*.

CONFIRMATION

The spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the peak due to atropine sulfate in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity

pH, 2.8 to 4.5, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For injections containing less than 0.1% w/v of Atropine Sulfate

(1) Use the injection being examined.

(2) Use *atropine sulfate BPCRS* and *homatropine hydrobromide BPCRS* in the mobile phase, both at the same concentration as the solution being examined.

For injections containing 0.1% w/v or more of Atropine Sulfate

(1) Dilute the injection, if necessary, to contain 0.1% w/v of Atropine Sulfate with *water*.

(2) 0.1% w/v of *atropine sulfate BPCRS* and 0.1% w/v of *homatropine hydrobromide BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 257 nm.

(f) For injections containing less than 0.1% w/v of Atropine Sulfate inject 100 µL of each solution. For injections containing 0.1% w/v or more of Atropine Sulfate inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium acetate* and 0.005M *dioctyl sodium sulfosuccinate* in *methanol (60%)* adjusted to pH 5.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to atropine sulfate and homatropine hydrobromide is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in the injection using the declared content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in *atropine sulfate BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atropine Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Anticholinergic.

DEFINITION

Atropine Oral Solution is a solution of Atropine Sulfate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of atropine sulfate, $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

For oral solutions containing less than 0.1% w/v of Atropine Sulfate

(1) Use the solution being examined.

(2) A solution of *atropine sulfate BPCRS* in *ethanol (96%)* at the same concentration as the solution being examined.

For oral solutions containing 0.1% w/v or more of Atropine Sulfate

(1) Evaporate a quantity of the oral solution containing 5 mg of Atropine Sulfate to dryness on a water bath, triturate the residue with 1 mL of *ethanol (96%)*, allow to stand and use the supernatant liquid.

(2) 0.5% w/v of *atropine sulfate BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat it at 105° for 20 minutes, allow to cool and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

10 volumes of *diethylamine*, 40 volumes of *acetone* and 50 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For oral solutions containing less than 0.1% w/v of Atropine Sulfate

(1) Use the solution being examined.
(2) A solution containing *atropine sulfate BPCRS* and *homatropine hydrobromide BPCRS* in the mobile phase, both at the same concentration as the solution being examined.

For oral solutions containing 0.1% w/v or more of Atropine Sulfate

(1) Dilute the oral solution with *water*, if necessary, to contain 0.1% w/v of Atropine Sulfate.
(2) 0.1% w/v of *atropine sulfate BPCRS* and 0.1% w/v of *homatropine hydrobromide BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 257 nm.
(f) For oral solutions containing less than 0.1% w/v of Atropine Sulfate, inject 100 µL of each solution. For injections containing 0.1% w/v or more of Atropine Sulfate, inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium acetate* and 0.005M *dioctyl sodium sulfosuccinate* in *methanol (60%)*, adjusted to pH 5.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to atropine sulfate and homatropine hydrobromide is at least 2.5.

Calculate the content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in the oral solution using the declared content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in *atropine sulfate BPCRS*.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

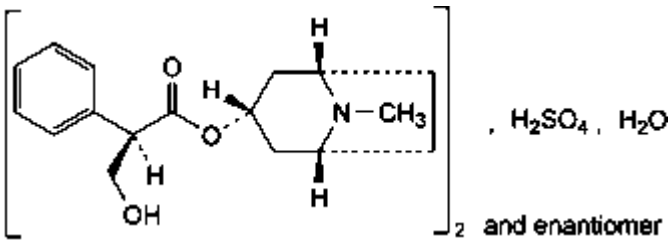
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atropine Sulfate

General Notices

Atropine Sulphate

(Ph. Eur. monograph 0068)



$C_{34}H_{48}N_2O_{10}S,H_2O$ 695 *5908-99-6*

Action and use

Anticholinergic.

Preparations

Atropine Eye Drops

Atropine Eye Ointment

Atropine Injection

Atropine Oral Solution

Atropine Tablets

Ph Eur

DEFINITION

Bis[(1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate] sulfate monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thietbiuocngocanh.com/

White or almost white, crystalline powder or colourless crystals.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B, E.

Second identification: C, D, E, F.

A. Optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *atropine sulfate CRS*.

C. Dissolve about 50 mg in 5 mL of *water R* and add 5 mL of *picric acid solution R*. The precipitate, washed with *water R* and dried at 100-105 °C for 2 h, melts (2.2.14) at 174 °C to 179 °C.

D. To about 1 mg add 0.2 mL of *fuming nitric acid R* and evaporate to dryness in a water-bath. Dissolve the residue in 2 mL of *acetone R* and add 0.1 mL of a 30 g/L solution of *potassium hydroxide R* in *methanol R*. A violet colour develops.

E. It gives the reactions of sulfates (2.3.1).

F. It gives the reaction of alkaloids (2.3.1).

TESTS

pH (2.2.3)

4.5 to 6.2.

Dissolve 0.6 g in *carbon dioxide-free water R* and dilute to 30 mL with the same solvent.

Optical rotation (2.2.7)

-0.50° to + 0.05° (measured in a 2 dm tube).

Dissolve 2.50 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 24 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 5 mg of *atropine impurity B CRS* in the test solution and dilute to 20 mL with the test solution. Dilute 5 mL of this solution to 25 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of *atropine for peak identification CRS* (containing impurities A, D, E, F, G and H) in 1 mL of mobile phase A.

Reference solution (d) Dissolve 5 mg of *tropic acid R* (impurity C) in mobile phase A and dilute to 10 mL with mobile phase A. Dilute 1 mL of the solution to 100 mL with mobile phase A. Dilute 1 mL of this solution to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *polar end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: dissolve 3.5 g of *sodium dodecyl sulfate R* in 606 mL of a 7.0 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.3 with a 5.8 g/L solution of *phosphoric acid R*, and mix with 320 mL of *acetonitrile R1*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	95	5
2 - 20	95 → 70	5 → 30

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *atropine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, D, E, F, G and H; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to atropine (retention time = about 11 min): impurity C = about 0.2; impurity E = about 0.67; impurity D = about 0.73; impurity F = about 0.8; impurity B = about 0.89; impurity H = about 0.93; impurity G = about 1.1; impurity A = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity B and atropine.

Limits:

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity C = 0.6;

— *impurities E, H*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities A, B, C, D, F, G*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

2.0 per cent to 4.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 30 mL of *anhydrous acetic acid R*, warming if necessary. Cool the solution. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

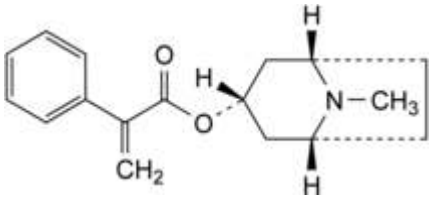
1 mL of *0.1 M perchloric acid* is equivalent to 67.68 mg of $C_{34}H_{48}N_2O_{10}S$.

STORAGE

Protected from light.

IMPURITIES

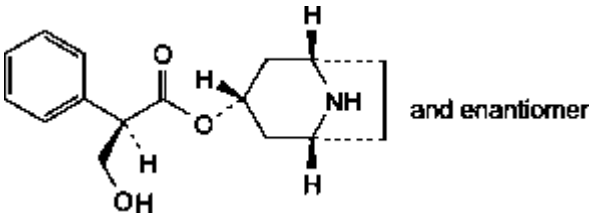
Specified impurities A, B, C, D, E, F, G, H.



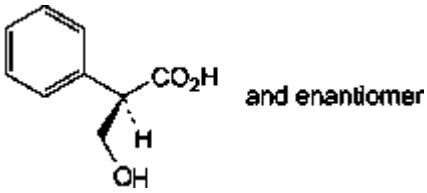
A. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 2-phenylpropenoate (apoatropine),

www.webofpharma.com

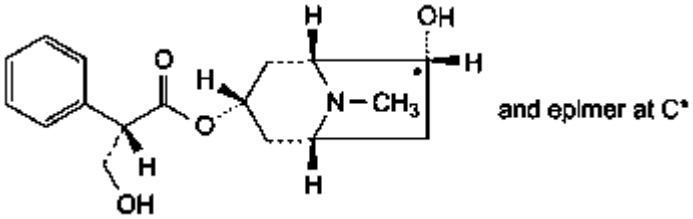
https://thuocngocanh.com/



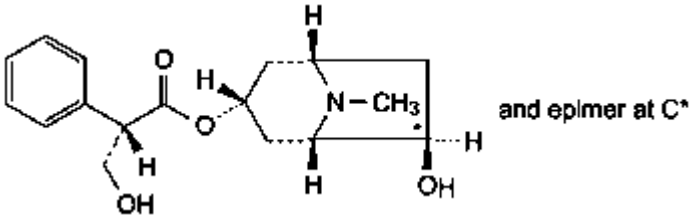
B. (1*R*,3*r*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate (noratropine),



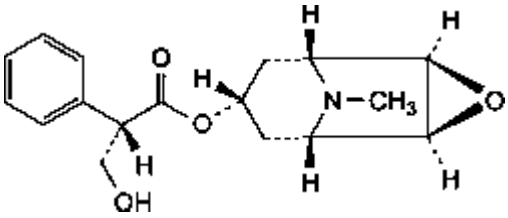
C. (2*RS*)-3-hydroxy-2-phenylpropanoic acid (tropic acid),



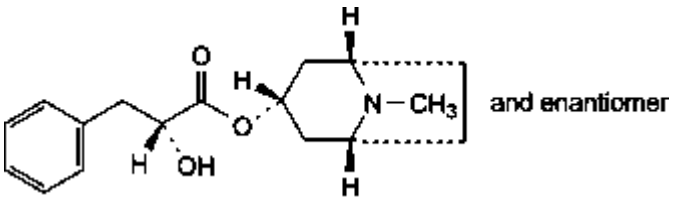
D. (1*R*,3*S*,5*R*,6*RS*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate (6-hydroxyhyoscyamine),



E. (1*S*,3*R*,5*S*,6*RS*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate (7-hydroxyhyoscyamine),



F. (1*R*,2*R*,4*S*,5*S*,7*s*)-9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate (hyoscine),



G. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-2-hydroxy-3-phenylpropanoate (littorine),

www.webofpharma.com

https://thietbiuocngocanh.com/

H. unknown structure.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Atropine Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Atropine Tablets contain Atropine Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of atropine sulfate, $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

(1) Shaking a quantity of the powdered tablets containing 10 mg of Atropine Sulfate with 2 mL of *ethanol (96%)*, centrifuge and use the supernatant liquid.

(2) 0.5% w/v of *atropine sulfate BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat it at 105° for 20 minutes, allow to cool and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

10 volumes of *diethylamine*, 40 volumes of *acetone* and 50 volumes of *chloroform*.

CONFIRMATION

The spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) exhibits a peak with the same retention time as the peak due to atropine sulfate in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thietbiuocngocanh.com/

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Atropine Sulfate comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 1 tablet with 2 ml of the mobile phase with the aid of ultrasound until fully disintegrated and filter.

(2) 0.03% w/v of *atropine sulfate BPCRS* and 0.03% w/v of *homatropine hydrobromide BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 257 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium acetate* and 0.005M *dioctyl sodium sulfosuccinate* in *methanol (60%)* adjusted to pH 5.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to atropine sulfate and homatropine hydrobromide is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in each tablet using the declared content of $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ in *atropine sulfate BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Attapulgite

General Notices

Action and use

Excipient.

DEFINITION

Attapulgite is a purified native hydrated magnesium aluminium silicate essentially consisting of the clay mineral palygorskite.

CHARACTERISTICS

A light, cream or buff, very fine powder, free or almost free from gritty particles.

IDENTIFICATION

A. Ignite 0.5 g with 2 g of *anhydrous sodium carbonate* for 20 minutes, cool and extract with 25 mL of boiling *water*. Cool, filter, wash the residue with *water* and add the washings to the filtrate. Reserve the residue for test B. Cautiously acidify the combined filtrate and washings with *hydrochloric acid*, evaporate to dryness, moisten the residue with 0.2 mL of *hydrochloric acid*, add 10 mL of *water* and stir. A white, gelatinous precipitate is produced.

B. Wash the residue reserved in test A with *water* and dissolve in 10 mL of *2M hydrochloric acid*. To 2 mL of the solution add a 10% w/v solution of *ammonium thiocyanate*. An intense red colour is produced.

C. To 2 mL of the solution obtained in test B add 1 mL of *strong sodium hydroxide solution* and filter. To the filtrate add 3 mL of *ammonium chloride solution*. A gelatinous white precipitate is produced.

D. To 2 mL of the solution obtained in test B add *ammonium chloride* and an excess of 13.5M *ammonia* and filter. To the filtrate add 0.15 mL of *magneson reagent* and an excess of 5M *sodium hydroxide*. A blue precipitate is produced.

TESTS

Acidity or alkalinity

pH of a 5% w/v suspension in *carbon dioxide-free water*, after shaking for 5 minutes, 7.0 to 9.5, Appendix V L.

Adsorptive capacity

Moisture adsorption, 5 to 14% when determined by the following method. Dry in air and powder a sufficient quantity of the substance being examined and pass through a sieve with a nominal mesh aperture of 150 µm. Spread 0.5 g as a thin layer on a previously weighed piece of aluminium foil (60 mm × 50 mm) of nominal gauge 17.5 µm and transfer to a desiccator containing a dish of sodium chloride crystals partially immersed in saturated brine at 25°. After 4 hours, remove from the desiccator and weigh immediately. Dry in an oven at 110° for 4

www.webofpharma.com

https://thuocngocanh.com/

hours, allow to cool in a desiccator and weigh. The *moisture adsorption* is the gain in weight of the substance being examined expressed as a percentage of its oven-dried weight.

Arsenic

To 0.13 g add 5 mL of *water*, 2 mL of *sulfuric acid* and 10 mL of *sulfur dioxide solution* and evaporate on a water bath until the sulfur dioxide solution is removed and the volume reduced to about 2 mL. Transfer the solution to the generator flask with the aid of 5 mL of *water*. The resulting solution complies with the *limit test for arsenic*, Appendix VII (8 ppm).

Acid-soluble matter

Boil 2 g with 100 mL of 0.2M *hydrochloric acid* under a reflux condenser for 5 minutes, cool and filter. Evaporate 50 mL of the filtrate to dryness. The residue, after ignition at about 600° for 30 minutes, weighs not more than 0.25 g.

Water-soluble matter

Boil 10 g with 100 mL of *water* under a reflux condenser for 5 minutes, cool and filter. Evaporate 50 mL of the filtrate to dryness. The residue, after ignition at 600° for 30 minutes, weighs not more than 50 mg.

Loss on drying

When dried to constant weight at 105°, loses not more than 17.0% of its weight. Use 1 g.

Loss on ignition

When ignited at 600°, loses 15.0 to 27.0% of its weight. Use 1 g.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

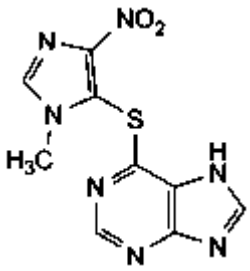
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azathioprine

General Notices

(Ph. Eur. monograph 0369)



$C_9H_7N_7O_2S$ 277.3 *446-86-6*

Action and use

Immunosuppressant.

Preparations

Azathioprine Oral Suspension

Azathioprine Tablets

Ph Eur

DEFINITION

6-[(1-Methyl-4-nitro-1*H*-imidazol-5-yl)sulfanyl]-7*H*-purine.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Pale-yellow powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water and in ethanol (96 per cent). It is soluble in dilute solutions of alkali hydroxides and sparingly soluble in dilute mineral acids.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison azathioprine CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solution A 2.76 g/L solution of sodium dihydrogen phosphate monohydrate R adjusted to pH 2.5 with phosphoric acid R.

Test solution Dissolve 10 mg of the substance to be examined in 35 mL of a 0.8 g/L solution of sodium hydroxide R and dilute to 100.0 mL with solution A.

Reference solution (a) Dissolve 5 mg of azathioprine impurity A CRS and 5 mg of mercaptopurine monohydrate R (impurity B) in 8.75 mL of a 0.8 g/L solution of sodium hydroxide R and dilute to 25.0 mL with solution A. To 1.0 mL of this solution, add 35 mL of a 0.8 g/L solution of sodium hydroxide R and dilute to 100.0 mL with solution A.

Reference solution (b) Dissolve 2.5 mg of azathioprine impurity G CRS and 2.5 mg of the substance to be examined in 8.8 mL of a 0.8 g/L solution of sodium hydroxide R and dilute to 25.0 mL with solution A. To 1.0 mL of this solution, add 17.5 mL of a 0.8 g/L solution of sodium hydroxide R and dilute to 50.0 mL with solution A.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: phenylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: methanol R, solution A (5:95 *V/V*);

— *mobile phase B*: solution A, methanol R (40:60 *V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 15	100 → 0	0 → 100
15 - 20	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B. Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to azathioprine (retention time = about 15 min): impurity A = about 0.3; impurity B = about 0.4; impurity G = about 0.97.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurities A and B in the chromatogram obtained with reference solution (a); minimum 2.0 between the peaks due to impurity G and azathioprine in the chromatogram obtained with reference solution (b).

Limits:

— *impurities A, B*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.250 g in 25 mL of *dimethylformamide R*. Titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M tetrabutylammonium hydroxide* is equivalent to 27.73 mg of $C_9H_7N_7O_2S$.

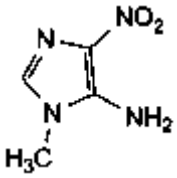
STORAGE

Protected from light.

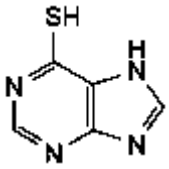
IMPURITIES

Specified impurities *A, B.*

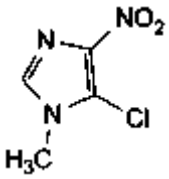
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F, G.*



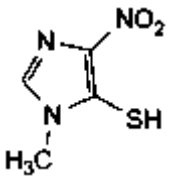
A. 1-methyl-4-nitro-1*H*-imidazol-5-amine,



B. 7*H*-purine-6-thiol (mercaptopurine),



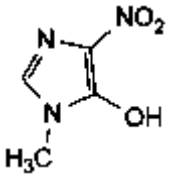
C. 5-chloro-1-methyl-4-nitro-1*H*-imidazole,



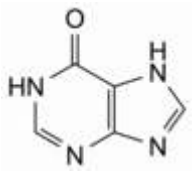
D. 1-methyl-4-nitro-1*H*-imidazole-5-thiol,

www.webofpharma.com

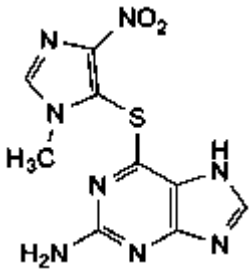
https://thuocngocanh.com/



E. 1-methyl-4-nitro-1*H*-imidazol-5-ol,



F. 1,7-dihydro-6*H*-purin-6-one (hypoxanthine),



G. 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)sulfanyl]-7*H*-purin-2-amine (thiamiprine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azathioprine Oral Suspension

General Notices

Different formulations of Azathioprine Oral Suspension may vary in bioavailability. Patients should be monitored in accordance with appropriate clinical guidelines.

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Immunosuppressant.

DEFINITION

Azathioprine Oral Suspension is a suspension of Azathioprine in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of azathioprine, $C_9H_7N_7O_2S$

95.0 to 105.0% of the stated amount.

Shake the oral suspension vigorously before carrying out the following tests.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions prepared immediately before use.

(1) Dilute a quantity of the oral suspension containing 40 mg of Azathioprine to 5 mL with *water* and then extract with three 20-mL quantities of *dichloromethane*. Combine the dichloromethane extracts, wash with 20 mL of *water*, discard the aqueous layer and evaporate the dichloromethane under a stream of nitrogen until about 5 mL remains.

(2) Disperse 40 mg of *azathioprine BPCRS* in 5 mL of *water* and then treat in the same manner as for solution (1) beginning at the words 'and then extract …'.

(3) 0.005% w/v of each of *azathioprine BPCRS* and *5-chloro-1-methyl-4-nitroimidazole BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *cellulose F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it at 50° and examine under *ultraviolet light (366 nm)*.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

butan-1-ol saturated with 6M *ammonia*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 6.5, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions, using 900 mL of *water* as the dissolution medium and rotating the paddle at 50 revolutions per minute. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the oral suspension containing 10 mg of Azathioprine with 12.5 mL of *dimethyl sulfoxide*, shake for 30 minutes and add sufficient *0.1M hydrochloric acid* to produce 25 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of equal volumes of *dimethyl sulfoxide* and *0.1M hydrochloric acid*.

(3) 0.004% w/v of each of *azathioprine BPCRS*, *5-chloro-1-methyl-4-nitroimidazole BPCRS* and *6-mercaptopurine* in a mixture of equal volumes of *dimethyl sulfoxide* and *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 300 volumes of *methanol* and 700 volumes of a 0.01M phosphate buffer prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water*.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase B 600 volumes of *methanol* and 400 volumes of a 0.01M phosphate buffer prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-30	100→0	0→100	linear gradient
30-40	0	100	isocratic
40-41	0→100	100→0	linear gradient
41-50	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the retention time of azathioprine is about 6.5 minutes;

there are peaks with retentions relative to azathioprine of about 0.53 (6-mercaptopurine) and about 1.14 (5-chloro-1-methyl-4-nitroimidazole).

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 5-chloro-1-methyl-4-nitroimidazole is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to 6-mercaptopurine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral suspension containing 0.1 g of Azathioprine to 50 mL with *dimethyl sulfoxide*, shake for 30 minutes and add sufficient *0.1M hydrochloric acid* to produce 250 mL.

(2) Dilute 5 volumes of a 0.08% w/v solution of *azathioprine BPCRS* in *dimethyl sulfoxide* to 10 volumes with *0.1M hydrochloric acid*.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

(g) Wash the column with *water* between injections.

MOBILE PHASE

300 volumes of *methanol* and 700 volumes of a 0.01M phosphate buffer prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_9H_7N_7O_2S$, weight in volume, using the declared content of $C_9H_7N_7O_2S$ in *azathioprine BPCRS*.

STORAGE

Azathioprine Oral Suspension should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azathioprine Tablets

General Notices

Action and use

Immunosuppressant.

DEFINITION

Azathioprine Tablets contain Azathioprine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of azathioprine, $C_9H_7N_7O_2S$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.2 g of Azathioprine with 50 mL of 6M *ammonia*, filter through a glass micro fibre paper (Whatman GF/C is suitable) and use the filtrate.

(2) 0.4% w/v of *azathioprine BPCRS* in 6M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *cellulose* F_{254}.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 20 cm.

(e) After removal of the plate, dry it at 50° and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

butan-1-ol saturated with 6M *ammonia*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Heat a quantity of the powdered tablets containing 20 mg of Azathioprine with 100 mL of *water* and filter. To 5 mL of the filtrate add 1 mL of *hydrochloric acid* and 10 mg of *zinc powder* and allow to stand for 5 minutes; a yellow colour is produced. Filter, cool in ice, add 0.1 mL of a 10% w/v solution of *sodium nitrite* and 0.1 g of *sulfamic acid* and shake until the bubbles disappear. Add 1 mL of *2-naphthol solution*; a pale pink precipitate is produced.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

5-Chloro-1-methyl-4-nitroimidazole and 6-mercaptopurine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.20 g of Azathioprine with 10 mL of 6M *ammonia* and filter through a glass micro fibre filter paper (Whatman GF/C is suitable).

(2) 2.0% w/v of *azathioprine BPCRS* and 0.020% w/v of *6-mercaptopurine* in 6M *ammonia*.

(3) 0.020% w/v of *6-mercaptopurine* in 6M *ammonia*.

(4) 0.020% w/v of *5-chloro-1-methyl-4-nitroimidazole BPCRS* in 6M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *cellulose* F_{254}.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 20 cm.

(e) After removal of the plate, dry it at 50° and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

butan-1-ol saturated with 6M *ammonia*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (2) shows two clearly separated spots.

LIMITS

Any spot in the chromatogram obtained with solution (1):

corresponding to 6-mercaptopurine in the chromatogram obtained with solution (2) is not more intense than the spot in the chromatogram obtained with solution (3);

any spot corresponding to 5-chloro-1-methyl-4-nitroimidazole in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.15 g of Azathioprine with 20 mL of *dimethyl sulfoxide* for 15 minutes and dilute to 500 mL with 0.1M *hydrochloric acid*. Avoid heating or the use of ultrasound. Filter, dilute 25 mL of the filtrate to 1000 mL with 0.1M *hydrochloric acid* and measure the *absorbance* of the resulting solution at the maximum at 280 nm, Appendix II B. Calculate the content of $C_9H_7N_7O_2S$ taking 628 as the value of A(1%, 1 cm) at the maximum at 280 nm.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Azathioprine Tablets should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

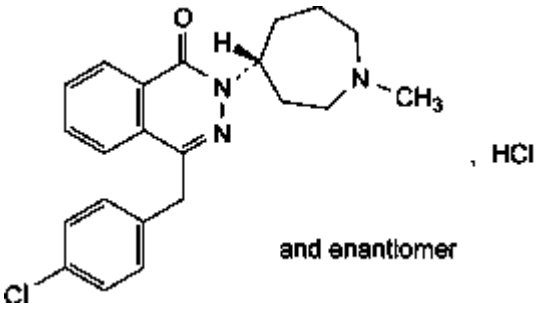
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azelastine Hydrochloride

General Notices

(Ph. Eur. monograph 1633)



$C_{22}H_{25}Cl_2N_3O$ 418.4 *79307-93-0*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

4-[(4-Chlorophenyl)methyl]-2-[(4*RS*)-1-methylhexahydro-1*H*-azepin-4-yl]phthalazin-1(2*H*)-one hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *azelastine hydrochloride CRS*.

B. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of *bromothymol blue solution R1*. Not more than 0.1 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R1*, *water for chromatography R* (45:55 *V/V*).

Test solution Dissolve 0.125 g of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 1 mg of *benzohydrazide R* (impurity A), 1 mg of *azelastine impurity B CRS*, 1 mg of *2-[2-(4-chlorophenyl)acetyl]benzoic acid R* (impurity C), 1 mg of *azelastine impurity D CRS* and 1 mg of *azelastine impurity E CRS* in the test solution and dilute to 20.0 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cyanosilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Dissolve 2.16 g of *sodium octanesulfonate R* and 0.68 g of *potassium dihydrogen phosphate R* in 740 mL of *water for chromatography R*; adjust to pH 3.0-3.1 with *dilute phosphoric acid R*, add 260 mL of *acetonitrile R1* and mix.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Run time 1.5 times the retention time of azelastine.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and E. The elution order may vary, especially for impurity E, but the peak area of each impurity in reference solution (b) is different, so a clear identification of the impurities is possible.

Relative retention With reference to azelastine (retention time = about 10 min): impurity A = about 0.2; impurity B = about 0.3; impurity C = about 0.4; impurity D = about 0.6; impurity E = about 0.8.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity E and azelastine and minimum 1.5 between the peaks due to impurities C and D in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 90 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.6; impurity B = 4.5; impurity C = 2.0; impurity E = 2.8;

— for each impurity, use the concentration of azelastine hydrochloride in reference solution (a).

Limits:

— *impurities A, B, C, E*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.300 g in 5 mL of *anhydrous formic acid R*. Add 30 mL of *acetic anhydride R*. Titrate quickly with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1.0 mL of *0.1 M perchloric acid* is equivalent to 41.84 mg of $C_{22}H_{25}Cl_2N_3O$.

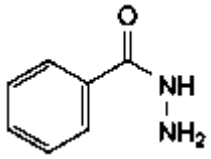
IMPURITIES

Specified impurities *A, B, C, E.*

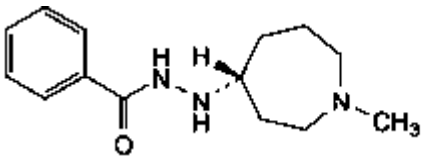
www.webofpharma.com

https://thuocngocanh.com/

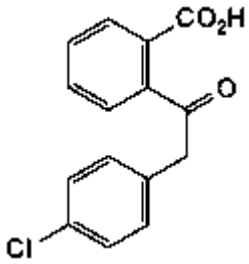
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D.



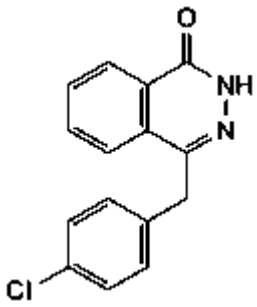
A. benzohydrazide (benzoyldiazane),



B. *N'*-[(4*RS*)-1-methylhexahydro-1*H*-azepin-4-yl]benzohydrazide,



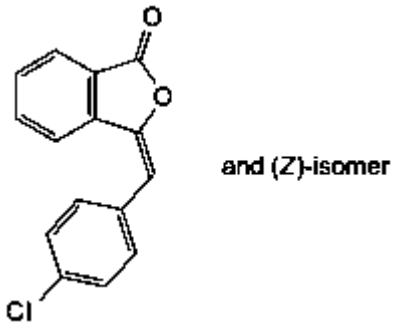
C. 2-[2-(4-chlorophenyl)acetyl]benzoic acid,



D. 4-[(4-chlorophenyl)methyl]phthalazin-1(2*H*)-one,

www.webofpharma.com

https://thuvienthuocngocanh.com/



E. (3*E*)-3-[(4-chlorophenyl)methylidene]-2-benzofuran-1(3*H*)-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

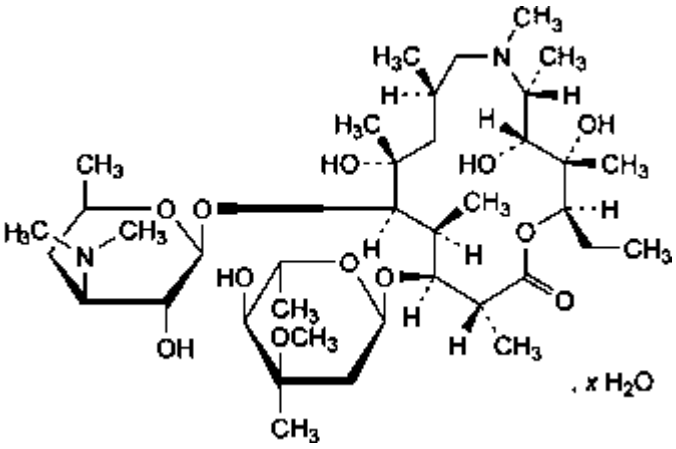
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azithromycin

General Notices

(Ph. Eur. monograph 1649)



$C_{38}H_{72}N_2O_{12},xH_2O$ with x = 1 or 2 749 (anhydrous substance)

Azithromycin monohydrate *121470-24-4*

Azithromycin dihydrate *117772-70-0*

Action and use

Macrolide antibacterial.

Preparations

Azithromycin Capsules

Azithromycin Eye Drops

Azithromycin for Infusion

Azithromycin Oral Suspension

Azithromycin Tablets

Ph Eur

DEFINITION

www.webofpharma.com

https://thuocngocanh.com/

(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. The degree of hydration is 1 or 2.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *azithromycin CRS*.

If the spectra obtained in the solid state show differences, prepare further spectra using 90 g/L solutions in *methylene chloride R*.

TESTS

Solution S

Dissolve 0.500 g in *anhydrous ethanol R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

9.0 to 11.0.

Dissolve 0.100 g in 25.0 mL of *methanol R* and dilute to 50.0 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

-49 to -45 (anhydrous substance), determined on solution S.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Solvent mixture Prepare a 1.73 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 10.0 with *ammonia R*. Transfer 350 mL of this solution to a suitable container. Add 300 mL of *acetonitrile R* and 350 mL of *methanol R*. Mix well.

Test solution Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *azithromycin for system suitability CRS* (containing impurities F, H and J) in 1.0 mL of the solvent mixture and sonicate for 5 min.

Reference solution (c) Dissolve 8.0 mg of *azithromycin for peak identification CRS* (containing impurities A, B, C, E, F, G, I, J, L, M, N, O and P) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (5 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: 1.80 g/L solution of *anhydrous disodium hydrogen phosphate R* adjusted to pH 8.9 with *dilute phosphoric acid R* or with *dilute sodium hydroxide solution R*;

— *mobile phase B*: *methanol R2*, *acetonitrile R1* (25:75 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	50 → 45	50 → 55
25 - 30	45 → 40	55 → 60
30 - 80	40 → 25	60 → 75
80 - 81	25 → 50	75 → 50
81 - 93	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *azithromycin for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, E, F, G, I, J, L, M, N, O and P; use the chromatogram supplied with *azithromycin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity H.

Relative retention With reference to azithromycin (retention time = 45-50 min): impurity L = about 0.29; impurity M = about 0.37; impurity E = about 0.43; impurity F = about 0.51; impurity D = about 0.54; impurity J = about 0.54; impurity Q = about 0.54; impurity I = about 0.61; impurity C = about 0.73; impurity N = about 0.76; impurity H = about 0.79; impurity A = about 0.83; impurity P = about 0.92; impurity O = about 1.23; impurity G = about 1.26; impurity B = about 1.31.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.4, where H_p = height above the baseline of the peak due to impurity J and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity F.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity F = 0.3; impurity G = 0.2; impurity H = 0.1; impurity L = 2.3; impurity M = 0.6; impurity N = 0.7;

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *impurities A, C, E, F, H, I, L, M, N, O, P*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *sum of impurities D, J and Q*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity G*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent); disregard the peaks eluting before impurity L and after impurity B.

Water (*2.5.12*)

1.8 per cent to 6.5 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Liquid chromatography (2.2.29).

Solution A Mix 60 volumes of acetonitrile R and 40 volumes of a 6.7 g/L solution of dipotassium hydrogen phosphate R adjusted to pH 8.0 with phosphoric acid R.

Test solution Dissolve 53.0 mg of the substance to be examined in 2 mL of acetonitrile R and dilute to 100.0 mL with solution A.

Reference solution (a) Dissolve 53.0 mg of azithromycin CRS in 2 mL of acetonitrile R and dilute to 100.0 mL with solution A.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of azithromycin impurity A CRS in 0.5 mL of acetonitrile R and dilute to 10 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl vinyl polymer for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 60 volumes of acetonitrile R1 and 40 volumes of a 6.7 g/L solution of dipotassium hydrogen phosphate R adjusted to pH 11.0 with a 560 g/L solution of potassium hydroxide R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Run time 1.5 times the retention time of azithromycin.

Retention time Azithromycin = about 10 min.

System suitability Reference solution (b):

— resolution: minimum 3.0 between the peaks due to impurity A and azithromycin.

Calculate the percentage content of $C_{38}H_{72}N_2O_{12}$ taking into account the assigned content of azithromycin CRS.

STORAGE

In an airtight container.

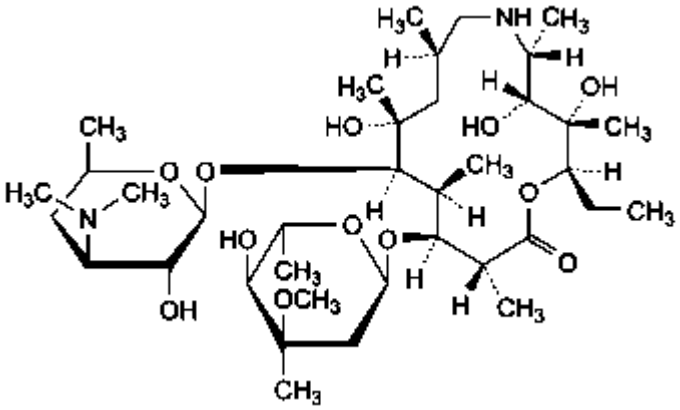
IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J, L, M, N, O, P, Q.*

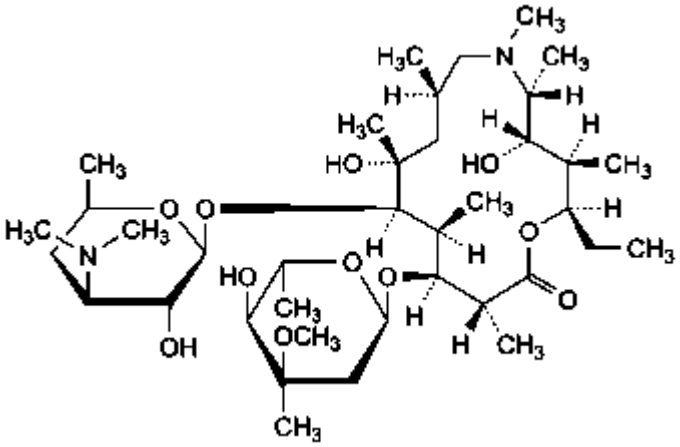
www.webofpharma.com

https://thuocngocanh.com/

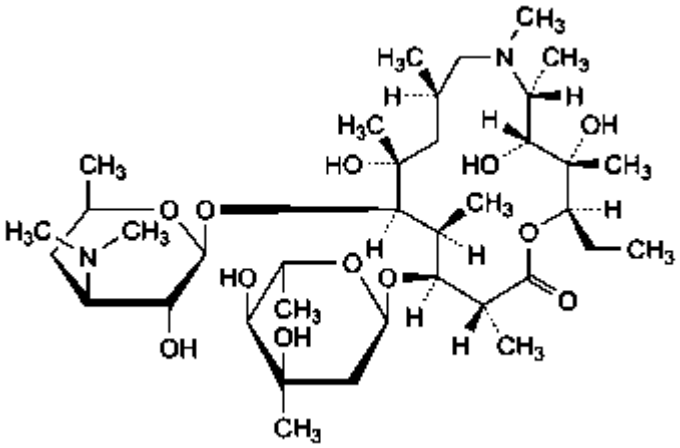
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) K.



A. 6-demethylazithromycin,



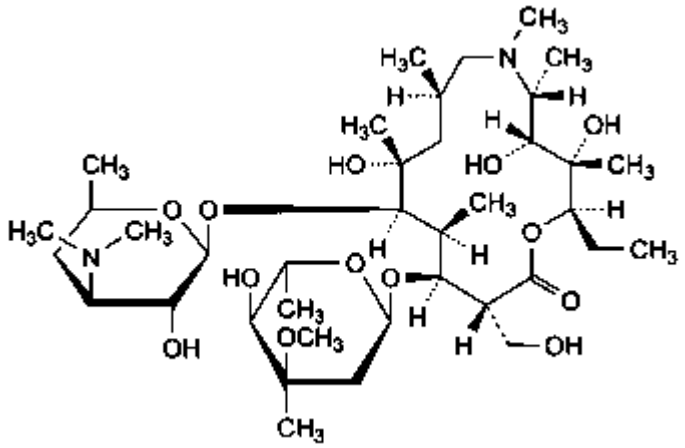
B. 3-deoxyazithromycin (azithromycin B),



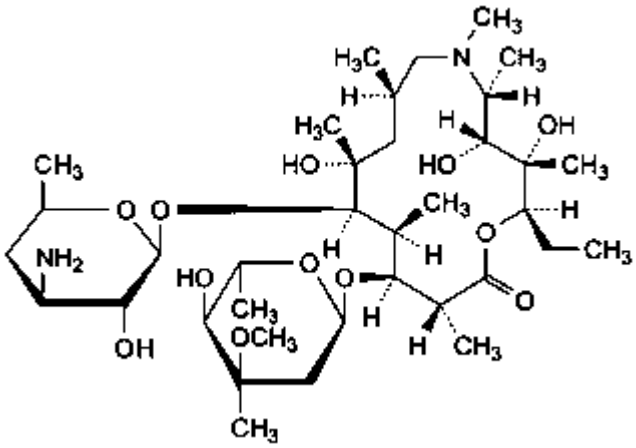
C. 3″-*O*-demethylazithromycin (azithromycin C),

www.webofpharma.com

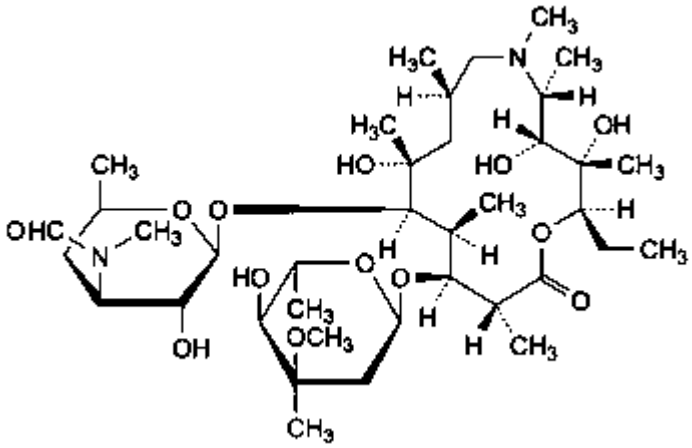
https://thuocngocanh.com/



D. 14-demethyl-14-(hydroxymethyl)azithromycin (azithromycin F),



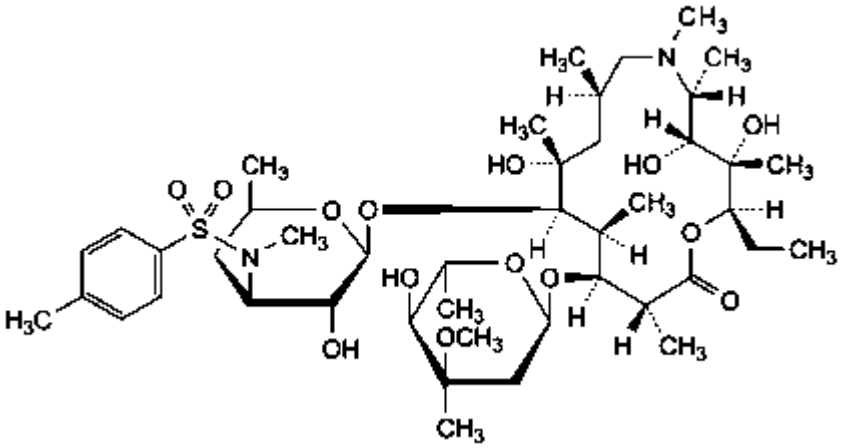
E. 3′-(*N*,*N*-didemethyl)azithromycin (aminoazithromycin),



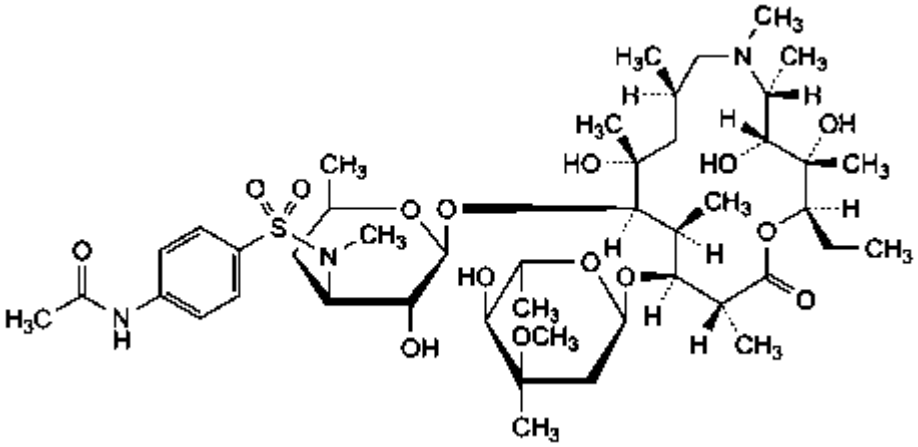
F. 3′-*N*-demethyl-3′-*N*-formylazithromycin,

www.webofpharma.com

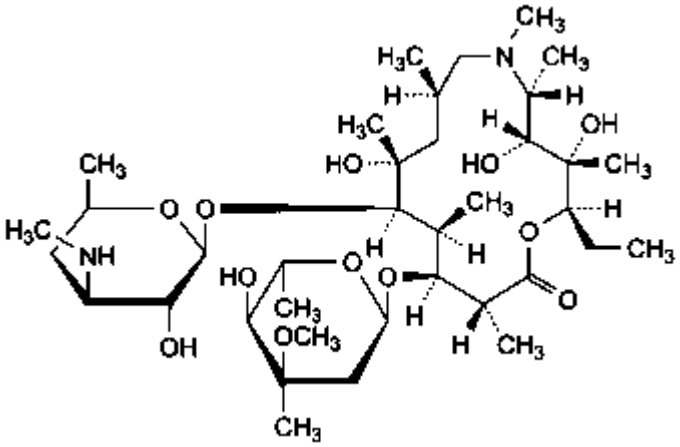
https://thuocngocanh.com/



G. 3′-*N*-demethyl-3′-*N*-[(4-methylphenyl)sulfonyl]azithromycin,



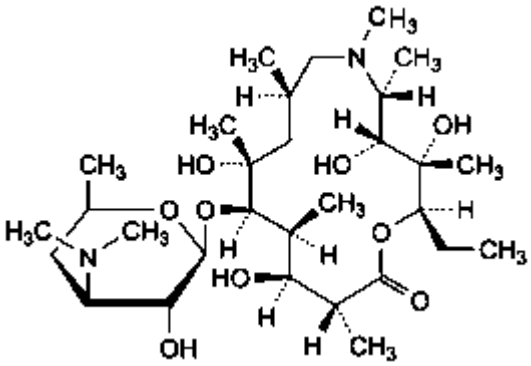
H. 3′-*N*-[[4-(acetylamino)phenyl]sulfonyl]-3′-*N*-demethylazithromycin,



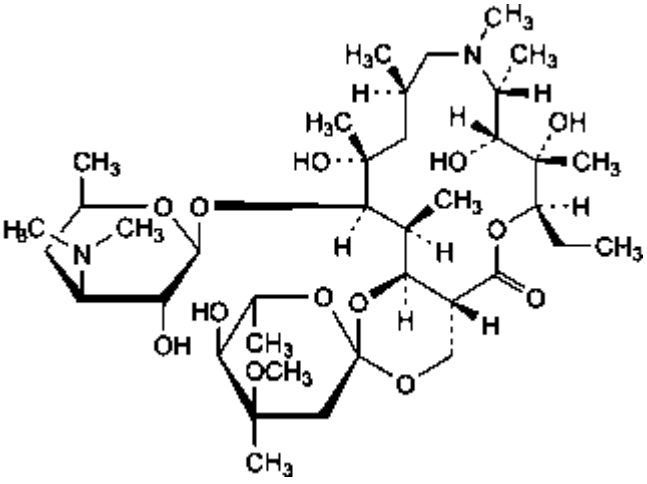
I. 3′-*N*-demethylazithromycin,

www.webofpharma.com

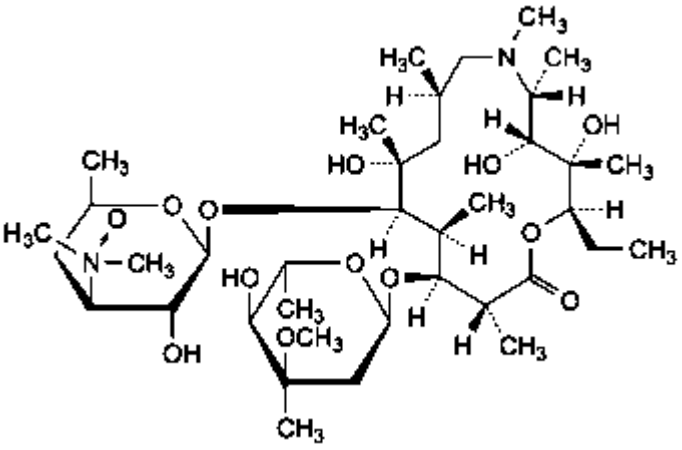
https://thuocngocanh.com/



J. 13-*O*-decladinosylazithromycin,



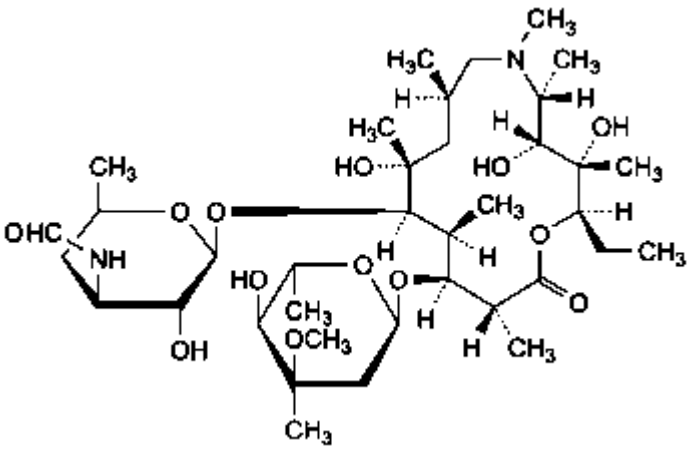
K. C^{14},1″-epoxyazithromycin (azithromycin E),



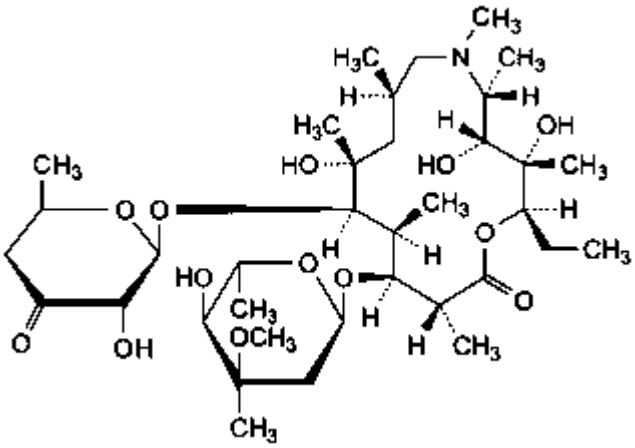
L. azithromycin 3′-*N*-oxide,

www.webofpharma.com

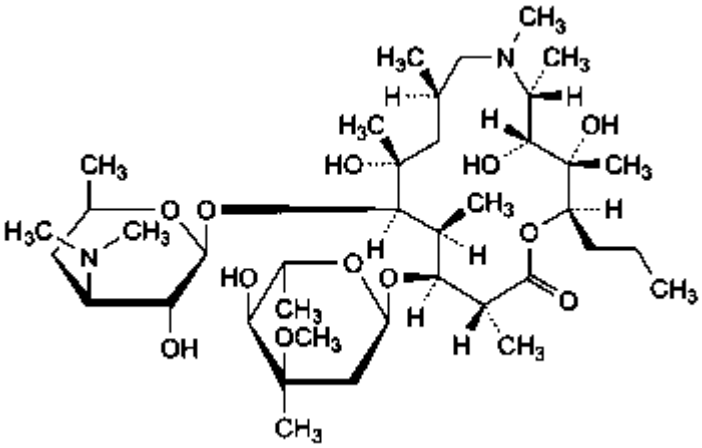
https://thuocngocanh.com/



M. 3′-(*N*,*N*-didemethyl)-3′-*N*-formylazithromycin,



N. 3′-de(dimethylamino)-3′-oxoazithromycin,

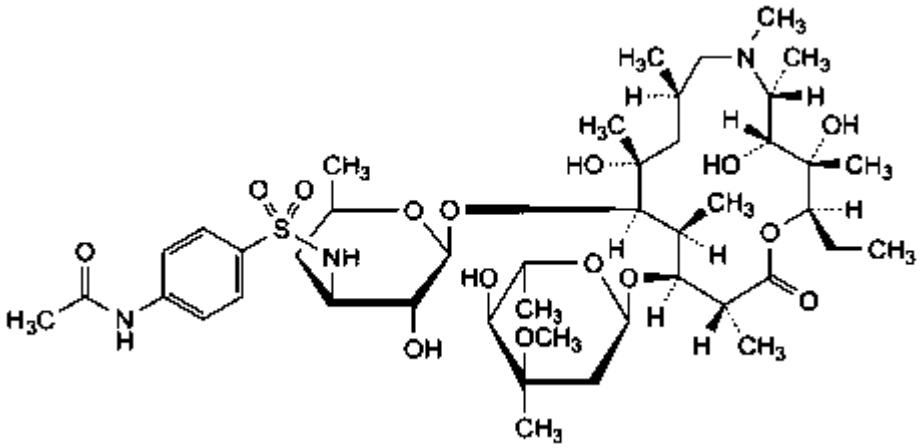


O. 2-desethyl-2-propylazithromycin,

P. unknown structure,

www.webofpharma.com

https://thuocngocanh.com/



Q. 3′-*N*-[[4-(acetylamino)phenyl]sulfonyl]-3′-(*N*,*N*-didemethyl)azithromycin.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azithromycin Capsules

General Notices

Action and use

Macrolide antibacterial.

DEFINITION

Azithromycin Capsules contain Azithromycin.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of azithromycin, $C_{38}H_{72}N_2O_{12}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the capsule contents containing 0.5 g of Azithromycin with 50 mL of *dichloromethane*. Filter (a 0.45-µm nylon filter is suitable) and evaporate the filtrate to dryness under a stream of nitrogen. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of azithromycin (*RS 487*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *sodium dihydrogen orthophosphate* previously adjusted to pH 6.0 with *sodium hydroxide* or *sodium hydroxide*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solvent A 40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 with *dilute phosphoric acid*, and 60 volumes of *acetonitrile R1*.

www.webofpharma.com

https://thietbiuocngocanh.com/

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute a quantity of the filtrate with the dissolution medium to produce a solution expected to contain 0.027% w/v of Azithromycin.

(2) 0.027% w/v of *azithromycin EPCRS* in the dissolution medium.

(3) 0.05% w/v each of *azithromycin EPCRS* and *azithromycin impurity A EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl vinyl polymer for chromatography* (5 µm) (Asahipak ODP-50 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 11.0 with a 56% w/v solution of *potassium hydroxide*, and 60 volumes of *acetonitrile R1*.

When the chromatograms are recorded under the prescribed conditions the retention time of azithromycin is about 10 minutes.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to azithromycin is between 0.8 and 2.0;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and azithromycin is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of azithromycin, $C_{38}H_{72}N_2O_{12}$, in the medium using the declared content of $C_{38}H_{72}N_2O_{12}$ in *azithromycin EPCRS*.

LIMITS

The amount of azithromycin, $C_{38}H_{72}N_2O_{12}$, released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions

Solvent B 35 volumes of a 0.173% w/v solution of *ammonium dihydrogen orthophosphate* adjusted to pH 10.0 with *ammonia*, 35 volumes of *methanol R1* and 30 volumes of *acetonitrile R1*.

(1) Shake a quantity of the capsule contents containing 0.2 g of Azithromycin with 15 mL of solvent B, dilute to 25 mL with the same solvent and filter (a 0.45-µm nylon filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent B.

www.webofpharma.com

https://thuocngocanh.com/

(3) Dissolve the contents of a vial of *azithromycin for system suitability EPCRS* in 1.0 mL of solvent B.

(4) 0.8% w/v of *azithromycin for peak identification EPCRS* in solvent B.

(5) Dilute 1 volume of solution (2) to 10 volumes with solvent B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for mass spectrometry* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.180% w/v solution of *anhydrous disodium hydrogen orthophosphate* adjusted to pH 8.9 with dilute *orthophosphoric acid* or with *dilute sodium hydroxide solution*.

Mobile phase B 25 volumes of *methanol R1* and 75 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	50→45	50→55	linear gradient
25-30	45→40	55→60	linear gradient
30-80	40→25	60→75	linear gradient
80-81	25→50	75→50	linear gradient
81-93	50	50	isocratic

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to azithromycin (Retention time about 45 minutes) are: impurity L, about 0.29; impurity M, about 0.37; impurity E, about 0.43; impurity F, about 0.51; impurity D, about 0.54; impurity J, about 0.54; impurity I, about 0.61; impurity C, about 0.73; impurity N, about 0.76; impurity H, about 0.79; impurity A, about 0.83; impurity P, about 0.92; impurity O, about 1.23; impurity G, about 1.26; impurity B, about 1.31.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.4, where Hp is the height above the baseline of the peak due to impurity J and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to Impurity F.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

identify any peaks corresponding to impurities F and H using solution (3) and any peaks corresponding to impurities G, L, M, and N using solution (4). Multiply the area of these peaks by corresponding correction factors: impurity F, 0.3, impurity H, 0.1; impurity G, 0.2; impurity L, 2.3, impurity M, 0.6; impurity N, 0.7;

the area of any peak due to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the areas of any peaks due to azithromycin impurities A, C, E, F, H, I, L, M, N, O, P is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any peaks due to impurities D and J is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peaks eluting before impurity L and after impurity B and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent C 40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 with *orthophosphoric acid* and 60 volumes of *acetonitrile R1*.

(1) Shake a quantity of the mixed contents of 20 capsules containing 0.5 g of Azithromycin with 40 mL of solvent C, dilute to 100 mL with the same solvent and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the filtrate to solution to 10 volumes with solvent C.
(2) 0.05% w/v of *azithromycin EPCRS* in solvent C.
(3) 0.05% w/v each of *azithromycin EPCRS* and *azithromycin impurity A EPCRS* in solvent C.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with an injection volume of 10 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and azithromycin is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of azithromycin, $C_{38}H_{72}N_2O_{12}$, in the capsules using the declared content of $C_{38}H_{72}N_2O_{12}$ in *azithromycin EPCRS*.

IMPURITIES

www.webofpharma.com

https://thuocngocanh.com/

The impurities limited by the requirements of this monograph include those listed under Azithromycin.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azithromycin Eye Drops

General Notices

Action and use

Macrolide antibacterial.

DEFINITION

Azithromycin Eye Drops are a sterile solution of Azithromycin in a suitable oily vehicle.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of azithromycin, $C_{38}H_{72}N_2O_{12}$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Add 10 mL of *absolute ethanol* to a quantity of the eye drops containing 0.1 g of Azithromycin and mix. Allow to stand, retain the upper ethanolic layer and evaporate it to dryness under a stream of nitrogen. Wash the residue with 10 mL of *hexane* followed by a further 50 mL of *hexane* and allow to dry in air. The *infrared absorption spectrum* of the dried residue, *Appendix II A*, is concordant with the reference spectrum of azithromycin (*RS 487*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *dichloromethane* and 80 volumes of *methanol*.

(1) Dilute a quantity of the eye drops, if necessary, to produce a solution containing 0.8% w/v of Azithromycin.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dissolve the contents of a vial of *azithromycin for system suitability EPCRS* in 1.0 mL.

(4) 0.8% w/v of *azithromycin for peak identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for mass spectrometry* (5 µm) (XTerra MS C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.18% w/v solution of *anhydrous disodium hydrogen orthophosphate* adjusted to pH 8.9 with dilute *orthophosphoric acid* or with *dilute sodium hydroxide solution*.

Mobile phase B 25 volumes of *methanol R1* and 75 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 - 25	50 → 45	50 → 55	linear gradient
25 - 30	45 → 40	55 → 60	linear gradient
30 - 80	40 → 25	60 → 75	linear gradient
80 - 81	25 → 50	75 → 50	linear gradient
81 - 93	50	50	re-equilabration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to azithromycin (retention time about 45 minutes) are: impurity L, about 0.29; impurity M, about 0.37; impurity E, about 0.43; impurity F, about 0.51; impurity D, about 0.54; impurity J, about 0.54; impurity I, about 0.61; impurity C, about 0.73; impurity N, about 0.76; impurity H, about 0.79; impurity A, about 0.83; impurity P, about 0.92; impurity O, about 1.23; impurity G, about 1.26; impurity B, about 1.31.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.4, where *Hp* is the height above the baseline of the peak due to impurity J and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity F.

LIMITS

In the chromatogram obtained with solution (1):

identify any peaks corresponding to impurities F and H using solution (3) and any peaks corresponding to impurities G, L, M, and N using solution (4). Multiply the area of these peaks by the corresponding correction factors: impurity F, 0.3; impurity H, 0.1; impurity G, 0.2; impurity L, 2.3; impurity M, 0.6; impurity N, 0.7;

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peaks corresponding to impurities A, C, E, F, H, I, L, M, N, O, P is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any peaks due to impurities D and J is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak eluting before impurity L and after impurity B and with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *dichloromethane* and 80 volumes of *methanol*.

(1) Dilute a weighed quantity of the eye drops to produce a solution containing 0.05% w/v of Azithromycin.
(2) 0.05% w/v of *azithromycin EPCRS*.
(3) 0.05% w/v each of *azithromycin EPCRS* and *azithromycin impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl vinyl polymer for chromatography* (5 µm) (Asahipak ODP-50 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature 40°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 11.0 with a 56% w/v solution of *potassium hydroxide*, and 60 volumes of *acetonitrile R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and azithromycin is at least 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the eye drops, *Appendix V G*, and calculate the total content of azithromycin, $C_{38}H_{72}N_2O_{12}$ in the eye drops using the declared content of $C_{38}H_{72}N_2O_{12}$ in *azithromycin EPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Azithromycin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azithromycin for Infusion

General Notices

Action and use

Macrolide antibacterial.

DEFINITION

Azithromycin for Infusion is a sterile material prepared from Azithromycin with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of azithromycin, $C_{38}H_{72}N_2O_{12}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the contents of the sealed container containing 0.5 g of Azithromycin in 50 mL of *dichloromethane*. Filter (a 0.45-µm nylon filter is suitable) and evaporate the filtrate to dryness under a stream of nitrogen. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of azithromycin (*RS 487*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolve the contents of one container in a suitable solvent as directed in the manufacturer's instructions. Further dilute with the same solvent to prepare a final solution containing 10% w/v of azithromycin and allow to stand for 30 minutes (solution A).

Acidity

The pH of solution A is 6.4 to 6.8, Appendix V L.

Clarity of solution

Solution A is not more opalescent than *reference suspension I*, Appendix IV A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

Solvent A 35 volumes of a 0.173% w/v solution of *ammonium dihydrogen orthophosphate* adjusted to pH 10.0 with *ammonia*, 35 volumes of *methanol R1* and 30 volumes of *acetonitrile R1*.

(1) Dissolve a quantity of the contents of the sealed container containing 0.2 g of Azithromycin in 15 mL of solvent A, dilute to 25 mL with the same solvent and filter (a 0.45-µm nylon filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A.

(3) Dissolve the contents of a vial of *azithromycin for system suitability EPCRS* in 1.0 mL of solvent A.

(4) 0.8% w/v of *azithromycin for peak identification EPCRS* in solvent A.

(5) Dilute 1 volume of solution (2) to 10 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for mass spectrometry* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.180% w/v solution of *anhydrous disodium hydrogen orthophosphate* adjusted to pH 8.9 with dilute *orthophosphoric acid* or with *dilute sodium hydroxide solution*.

Mobile phase B *25 volumes of* *methanol R1* and 75 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	50→45	50→55	linear gradient
25-30	45→40	55→60	linear gradient
30-80	40→25	60→75	linear gradient
80-81	25→50	75→50	linear gradient
81-93	50	50	isocratic

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to azithromycin (Retention time about 45 minutes) are: impurity L, about 0.29; impurity M, about 0.37; impurity E, about 0.43; impurity F, about 0.51; impurity D, about 0.54; impurity J, about 0.54; impurity I, about 0.61; impurity C, about 0.73; impurity N, about 0.76; impurity H, about 0.79; impurity A, about 0.83; impurity P, about 0.92; impurity O, about 1.23; impurity G, about 1.26; impurity B, about 1.31.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.4, where Hp is the height above the baseline of the peak due to impurity J and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to Impurity F.

LIMITS

In the chromatogram obtained with solution (1):

identify any peaks corresponding to impurities F and H using solution (3) and any peaks corresponding to impurities G, L, M, and N using solution (4). Multiply the area of these peaks by corresponding correction factors: impurity F, 0.3, impurity H, 0.1; impurity G, 0.2; impurity L, 2.3, impurity M, 0.6; impurity N, 0.7;

the area of any peak due to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the areas of any peaks due to azithromycin impurities A, C, E, F, H, I, L, M, N, O, P is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any peaks due to impurities D and J is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peaks eluting before impurity L and after impurity B and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

Water

Not more than 3.0% w/w, Appendix IX C. Method I. Use 0.5 g.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent B 40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 with *orthophosphoric acid* and 60 volumes of *acetonitrile R1*.

(1) Dissolve a quantity of the mixed contents of the 10 containers containing 0.5 g of Azithromycin in 50 mL of solvent B, dilute to 100 mL with the same solvent and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the filtrate to solution to 10 volumes with solvent B.
(2) 0.05% w/v of *azithromycin EPCRS* in solvent B.
(3) 0.05% w/v each of *azithromycin EPCRS* and *azithromycin impurity A EPCRS* in solvent B.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl vinyl polymer for chromatography* (5 µm) (Asahipak ODP-50 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 11.0 with a 56% w/v solution of *potassium hydroxide*, and 60 volumes of acetonitrile *R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and azithromycin is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of azithromycin, $C_{38}H_{72}N_2O_{12,}$ in a container of average content weight using the declared content of $C_{38}H_{72}N_2O_{12}$ in *azithromycin EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Azithromycin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Azithromycin Tablets

General Notices

Action and use

Macrolide antibacterial.

DEFINITION

Azithromycin Tablets contain Azithromycin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of azithromycin, $C_{38}H_{72}N_2O_{12}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Azithromycin with 50 mL of *dichloromethane*. Filter (a 0.45-µm nylon filter is suitable) and evaporate the filtrate to dryness under a stream of nitrogen. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of azithromycin (*RS 487*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *sodium dihydrogen orthophosphate* previously adjusted to pH 6.0 with *sodium hydroxide*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solvent A 40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 with *orthophosphoric acid* and 60 volumes of *acetonitrile R1*.

www.webofpharma.com

https://thuocngocanh.com/

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute a quantity of the filtrate with the dissolution medium to produce a solution expected to contain 0.027% w/v of Azithromycin.

(2) 0.027% w/v of *azithromycin EPCRS* in the dissolution medium.

(3) 0.05% w/v each of *azithromycin EPCRS* and *azithromycin impurity A EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl vinyl polymer for chromatography* (5 µm) (Asahipak ODP-50 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 11.0 with a 56% w/v solution of *potassium hydroxide*, and 60 volumes of *acetonitrile R1*.

When the chromatograms are recorded under the prescribed conditions the retention time of azithromycin is about 10 minutes.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2) the *symmetry factor* of the peak due to azithromycin is between 0.8 and 2.0;

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and azithromycin is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of azithromycin, $C_{38}H_{72}N_2O_{12}$, in the medium using the declared content of $C_{38}H_{72}N_2O_{12}$ in *azithromycin EPCRS*.

LIMITS

The amount of azithromycin, $C_{38}H_{72}N_2O_{12}$, released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent B 35 volumes of a 0.173% w/v solution of *ammonium dihydrogen orthophosphate* adjusted to pH 10.0 with *ammonia*, 35 volumes of *methanol R1* and 30 volumes of *acetonitrile R1*.

(1) Shake a quantity of powdered tablets containing 0.2 g of Azithromycin with 15 mL of solvent B, dilute to 25 mL with the same solvent and filter (a 0.45-µm nylon filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent B.

www.webofpharma.com

https://thuocngocanh.com/

(3) Dissolve the contents of a vial of *azithromycin for system suitability EPCRS* in 1.0 mL of solvent B.

(4) 0.8% w/v of *azithromycin for peak identification EPCRS* in solvent B.

(5) Dilute 1 volume of solution (2) to 10 volumes with solvent B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for mass spectrometry* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.180% w/v solution of *anhydrous disodium hydrogen orthophosphate* adjusted to pH 8.9 with dilute *orthophosphoric acid* or with *dilute sodium hydroxide solution*.

Mobile phase B 25 volumes of *methanol R1* and 75 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	50→45	50→55	linear gradient
25-30	45→40	55→60	linear gradient
30-80	40→25	60→75	linear gradient
80-81	25→50	75→50	linear gradient
81-93	50	50	isocratic

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to azithromycin (Retention time about 45 minutes) are: impurity L, about 0.29; impurity M, about 0.37; impurity E, about 0.43; impurity F, about 0.51; impurity D, about 0.54; impurity J, about 0.54; impurity I, about 0.61; impurity C, about 0.73; impurity N, about 0.76; impurity H, about 0.79; impurity A, about 0.83; impurity P, about 0.92; impurity O, about 1.23; impurity G, about 1.26; impurity B, about 1.31.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.4, where Hp is the height above the baseline of the peak due to impurity J and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to Impurity F.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

identify any peaks corresponding to impurities F and H using solution (3) and any peaks corresponding to impurities G, L, M, and N using solution (4). Multiply the area of these peaks by corresponding correction factors: impurity F, 0.3, impurity H, 0.1; impurity G, 0.2; impurity L, 2.3, impurity M, 0.6; impurity N, 0.7;

the area of any peak due to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the areas of any peaks due to azithromycin impurities A, C, E, F, H, I, L, M, N, O, P is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any peaks due to impurities D and J is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak eluting before impurity L and after impurity B and with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent C 40 volumes of a 0.67% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 with *orthophosphoric acid* and 60 volumes of *acetonitrile R1*.

(1) Shake a quantity of the powdered tablets containing 0.5 g of Azithromycin with 40 mL of solvent C, dilute to 100 mL with the same solvent and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the filtrate to 10 volumes with solvent C.
(2) 0.05% w/v of *azithromycin EPCRS* in solvent C.
(3) 0.05% w/v each of *azithromycin EPCRS* and *azithromycin impurity A EPCRS* in solvent C.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with an injection volume of 10 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and azithromycin is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of azithromycin, $C_{38}H_{72}N_2O_{12}$ in the tablets using the declared content of $C_{38}H_{72}N_2O_{12}$ in *azithromycin EPCRS*.

IMPURITIES

www.webofpharma.com

https://thietbiuocngocanh.com/

The impurities limited by the requirements of this monograph include those listed under Azithromycin.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

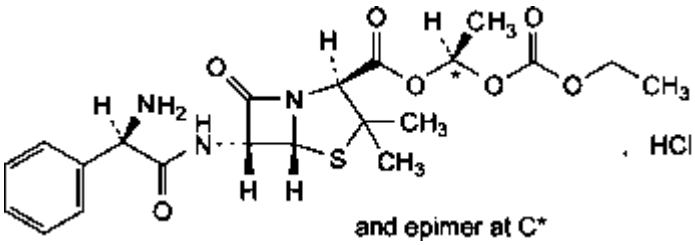
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bacampicillin Hydrochloride

General Notices

(Ph. Eur. monograph 0808)



$C_{21}H_{28}ClN_3O_7S$ 502.0 *37661-08-8*

Action and use

Penicillin antibacterial.

Ph Eur

DEFINITION

(1*RS*)-1-[(Ethoxycarbonyl)oxy]ethyl (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate hydrochloride.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder or granules, hygroscopic.

Solubility

Soluble in water, freely soluble in ethanol (96 per cent), soluble in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *bacampicillin hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 2 mL of *methanol R*.

Reference solution (a) Dissolve 10 mg of *bacampicillin hydrochloride CRS* in 2 mL of *methanol R*.

Reference solution (b) Dissolve 10 mg of *bacampicillin hydrochloride CRS*, 10 mg of *talampicillin hydrochloride CRS* and 10 mg of *pivampicillin CRS* in 2 mL of *methanol R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 10 volumes of a 272 g/L solution of *sodium acetate R* adjusted to pH 5.0 with *glacial acetic acid R*, 40 volumes of *water R* and 50 volumes of *ethanol (96 per cent) R*.

Application 1 µL.

Development Over a path of 15 cm.

Drying In a current of warm air.

Detection Spray with *ninhydrin solution R1* and heat at 60 °C for 10 min.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube on a water-bath for 1 min; a dark yellow colour develops.

D. Dissolve about 25 mg in 2 mL of *water R*. Add 2 mL of *dilute sodium hydroxide solution R* and shake. Wait a few minutes and add 3 mL of *dilute nitric acid R* and 0.5 mL of *silver nitrate solution R1*. A white precipitate is formed. Add 0.5 mL of *concentrated ammonia R*. The precipitate dissolves.

TESTS

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.200 g in 20 mL of *water R*; the solution is not more opalescent than reference suspension II (*2.2.1*). Dissolve 0.500 g in 10 mL of *water R*; the absorbance (*2.2.25*) of the solution at 430 nm is not greater than 0.10.

pH (*2.2.3*)

3.0 to 4.5.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 175 to + 195 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the test solution and reference solutions (a), (b) and (d) immediately before use.*

Phosphate buffer A Dissolve 1.4 g of *sodium dihydrogen phosphate monohydrate R* in *water R* and dilute to about 800 mL with the same solvent. Adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000.0 mL with *water R*.

Phosphate buffer B Dissolve 2.75 g of *sodium dihydrogen phosphate monohydrate R* and 2.3 g of *disodium hydrogen phosphate dihydrate R* in *water R* and dilute to about 1800 mL with the same solvent. Adjust to pH 6.8, if necessary, using *dilute phosphoric acid R* or *dilute sodium hydroxide solution R* and dilute to 2000.0 mL with *water R*.

Test solution Dissolve 30.0 mg of the substance to be examined in phosphate buffer A and dilute to 100.0 mL with phosphate buffer A.

Reference solution (a) Dissolve 30.0 mg of *bacampicillin hydrochloride CRS* in phosphate buffer A and dilute to 100.0 mL with phosphate buffer A.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with phosphate buffer A.

Reference solution (c) Dissolve 30 mg of the substance to be examined in phosphate buffer B and dilute to 100 mL with phosphate buffer B. Heat at 80 °C for about 30 min.

Reference solution (d) Dissolve 20 mg of *ampicillin trihydrate CRS* (impurity I) in phosphate buffer A and dilute to 250 mL with phosphate buffer A. Dilute 5 mL of this solution to 100 mL with phosphate buffer A.

Column:

— *size*: *l* = 0.05 m, Ø = 3.9 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 30 volumes of *acetonitrile R1* and 70 volumes of a 0.06 per cent *m/m* solution of *tetrahexylammonium hydrogen sulfate R* in phosphate buffer B.

Flow rate 1.0 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 3.5 times the retention time of bacampicillin.

System suitability:

— the peak due to impurity I is separated from the peaks due to the solvent in the chromatogram obtained with reference solution (d);

— *relative retention* with reference to bacampicillin: degradation product eluting just after bacampicillin = 1.12 to 1.38 in the chromatogram obtained with reference solution (c); if necessary, adjust the concentration of tetrahexylammonium hydrogen sulfate in the mobile phase.

Limits:

— *any impurity*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Butyl acetate and ethyl acetate (*2.4.24, System A*)

Maximum 2.0 per cent of butyl acetate, maximum 4.0 per cent of ethyl acetate and maximum 5.0 per cent for the sum of the contents.

Sample solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Use the method of standard additions.

Static head-space conditions that may be used:

— *equilibration temperature*: 60 °C;

— *equilibration time*: 20 min.

N,*N*-Dimethylaniline (*2.4.26, Method A*)

Maximum 20 ppm.

Water (*2.5.12*)

Maximum 0.8 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 1.5 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

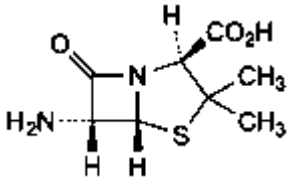
— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{21}H_{28}ClN_3O_7S$ from the declared content of *bacampicillin hydrochloride CRS*.

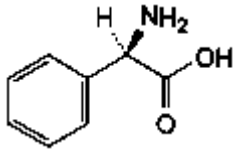
STORAGE

In an airtight container.

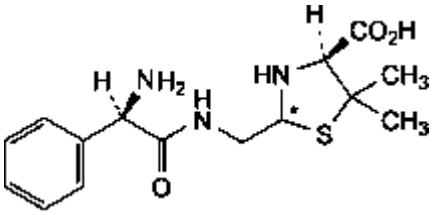
IMPURITIES



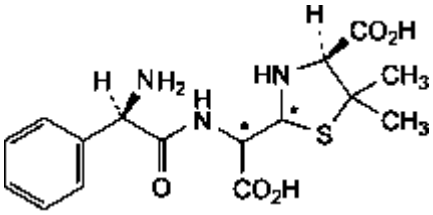
A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



B. (2*R*)-2-amino-2-phenylacetic acid (D-phenylglycine),



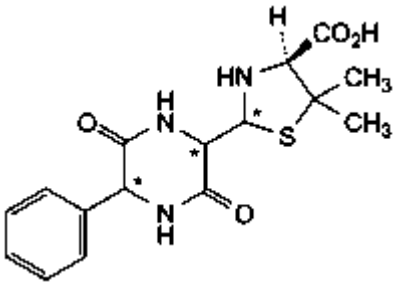
C. (2*RS*,4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of ampicillin),



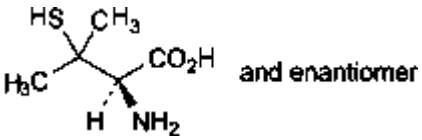
D. (4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of ampicillin),

www.webofpharma.com

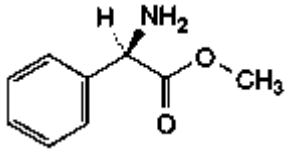
https://thuocngocanh.com/



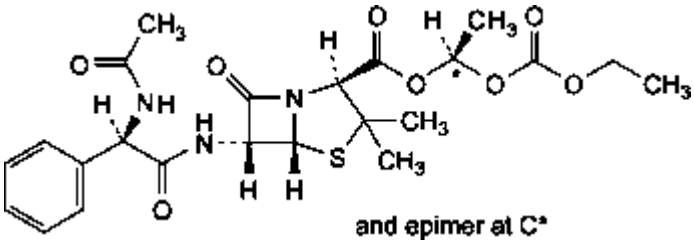
E. (4*S*)-2-(3,6-dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid (diketopiperazines of ampicillin),



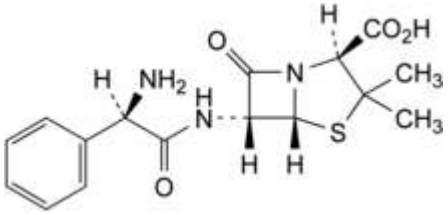
F. (2*RS*)-2-amino-3-methyl-3-sulfanylbutanoic acid (DL-penicillamine),



G. methyl (2*R*)-2-amino-2-phenylacetate (methyl D-phenylglycinate),



H. (1*RS*)-1-[(ethoxycarbonyl)oxy]ethyl (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-(acetylamino)-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (*N*-acetylbacampicillin),



I. (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (ampicillin).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

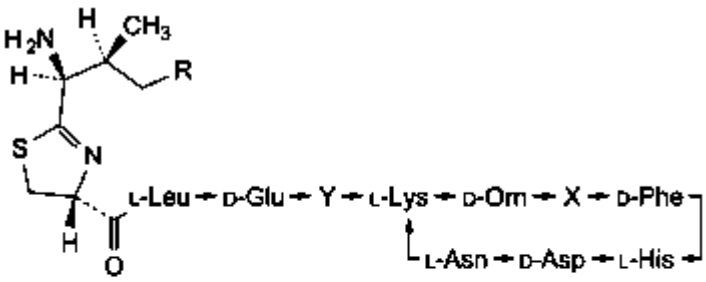
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bacitracin

General Notices

(Ph. Eur. monograph 0465)



Name	Mol. Formula	X	Y	R
Bacitracin A	$C_{66}H_{103}N_{17}O_{16}S$	L-Ile	L-Ile	CH_3
Bacitracin B1	$C_{65}H_{101}N_{17}O_{16}S$	L-Ile	L-Ile	H
Bacitracin B2	$C_{65}H_{101}N_{17}O_{16}S$	L-Val	L-Ile	CH_3
Bacitracin B3	$C_{65}H_{101}N_{17}O_{16}S$	L-Ile	L-Val	CH_3

1405-87-4

Action and use

Polypeptide antibacterial.

Ph Eur

DEFINITION

Mixture of antimicrobial polypeptides produced by certain strains of *Bacillus licheniformis* or *Bacillus subtilis*, the main components being:

— 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin A);

— 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*)-1-amino-2-methylpropyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin B1);

— 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin B2);

— 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin B3).

Content

www.webofpharma.com

https://thuocngocanh.com/

Content

Minimum 60 IU/mg (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, C.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a 3.4 g/L solution of *hydrochloric acid R* and dilute to 1.0 mL with the same solution.

Reference solution Dissolve 10 mg of *bacitracin zinc CRS* in a 3.4 g/L solution of *hydrochloric acid R* and dilute to 1.0 mL with the same solution.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (14:29:57 *V/V/V*).

Application 10 µL.

Development Over half of the plate.

Drying At 100-105 °C.

Detection Spray with *ninhydrin solution R1* and heat at 110 °C for 5 min.

Results The spots in the chromatogram obtained with the test solution are similar in position, size and colour to the spots in the chromatogram obtained with the reference solution.

B. Composition (see Tests).

C. Ignite 0.2 g. There is no significant yellow-coloured residue at high temperature. Allow to cool. Dissolve the residue in 0.1 mL of *dilute hydrochloric acid R*. Add 5 mL of *water R* and 0.2 mL of *strong sodium hydroxide solution R*. No white precipitate is formed.

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.25 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*).

pH (*2.2.3*)

6.0 to 7.0 for solution S.

Composition

Liquid chromatography (*2.2.29*): use the normalisation procedure. *Prepare the solutions immediately before use.*

Solution A 40 g/L solution of *sodium edetate R* adjusted to pH 7.0 with *dilute sodium hydroxide solution R*.

Solution B In a volumetric flask, dissolve 54.4 g of *potassium dihydrogen phosphate R* in *water for chromatography R* and dilute to 2000 mL with the same solvent. Adjust to pH 6.0 with a 34.8 g/L solution of *dipotassium hydrogen phosphate R* and filter through a membrane filter (nominal pore size 0.45 µm).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 20.0 mg of *bacitracin for system suitability CRS* in solution A and dilute to 10.0 mL with the same solution.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (c) In order to prepare impurities E, F, G and H *in situ*, heat about 4 mL of reference solution (a) in a water-bath for 30 min. Cool to room temperature.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 28 ± 2 °C.

Mobile phase *acetonitrile R*, solution B, *water for chromatography R*, *methanol R* (43:100:300:557 *V/V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 100 µL of the test solution and reference solutions (a) and (b).

Run time 3 times the retention time of bacitracin A.

Identification of peaks Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurity M and bacitracins A, B1, B2 and B3 (see Figure 0465.-1).

www.webofpharma.com

https://thuvienthuocngocanh.com/

Relative retention With reference to bacitracin A (retention time = about 20 min): impurity A = about 0.44; impurity B = about 0.52; impurity C = about 0.55; bacitracin B1 = about 0.65; bacitracin B2 = about 0.67; bacitracin B3 = about 0.81; impurity M = about 0.87; impurity N = about 0.90; impurity L = about 0.93; impurity O = about 1.2; impurities P and Q = about 1.3; impurity F = about 1.6; impurity G = about 1.8; impurity H = about 2.1; impurity E = about 2.8.

If necessary, adjust the composition of the mobile phase by changing the amount of organic modifier whilst keeping the ratio constant between methanol and acetonitrile.

System suitability:

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to bacitracin B2 and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to bacitracin B1 in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.1, where H_p = height above the baseline of the peak due to impurity M and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to bacitracin B3 in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 50 for the peak due to bacitracin A in the chromatogram obtained with reference solution (b).

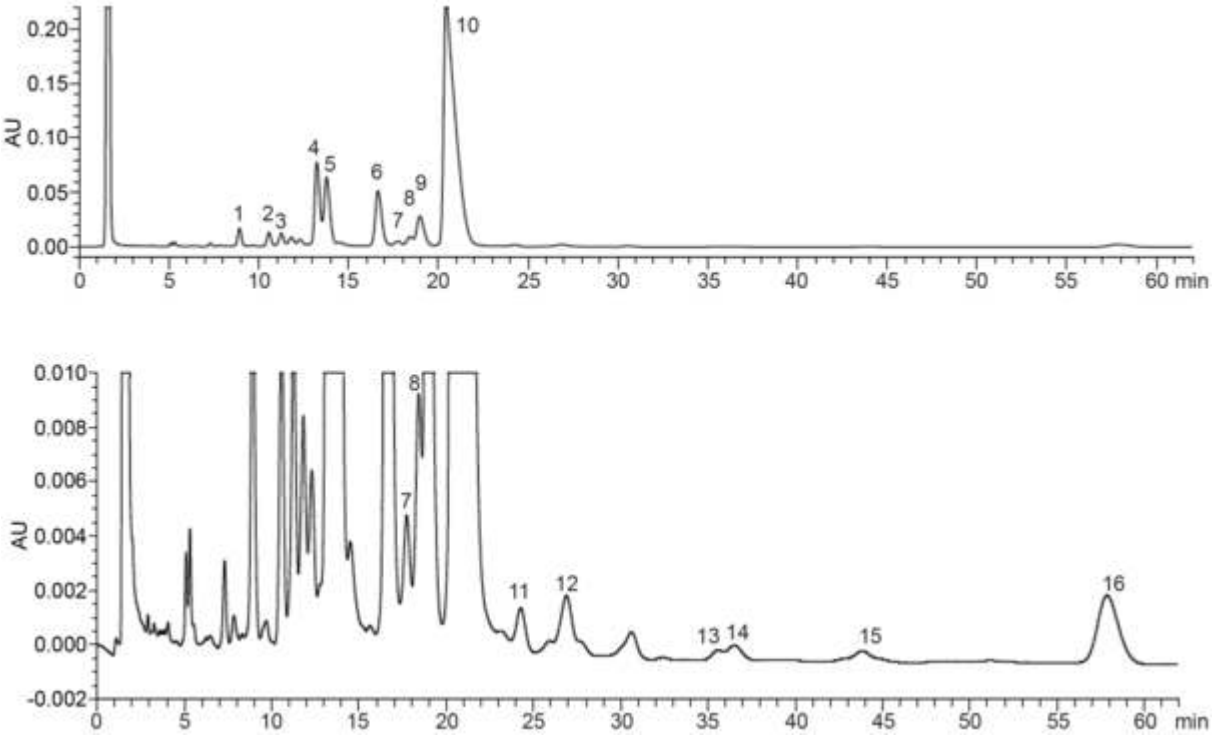
Limits:

— *bacitracin A*: minimum 45.0 per cent;

— *sum of bacitracins A, B1, B2 and B3*: minimum 77.0 per cent;

— *reporting threshold*: 0.25 per cent.

https://thuocngocanh.com/



1. impurity A	5. bacitracin B2	9. impurity L	13. impurity F
2. impurity B	6. bacitracin B3	10. bacitracin A	14. impurity G
3. impurity C	7. impurity M	11. impurity O	15. impurity H
4. bacitracin B1	8. impurity N	12. impurities P and Q	16. impurity E

Figure 0465.-1. – *Chromatogram for the test for composition of bacitracin: test solution*

Related substances

Liquid chromatography (2.2.29) as described in the test for composition with the following modifications. Use the normalisation procedure.

Injection Test solution and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, L, M, N, O, P and Q (see Figure 0465.-1); use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities E, F, G and H (see Figure 0465.-2).

Limits:

— *sum of impurities L and N*: maximum 8.0 per cent;

— *impurity E*: maximum 4.0 per cent;

— *impurity A*: maximum 3.5 per cent;

— *impurities B, M*: for each impurity, maximum 3.0 per cent;

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *impurity C*: maximum 2.5 per cent;

— *sum of impurities O, P and Q*: maximum 2.5 per cent;

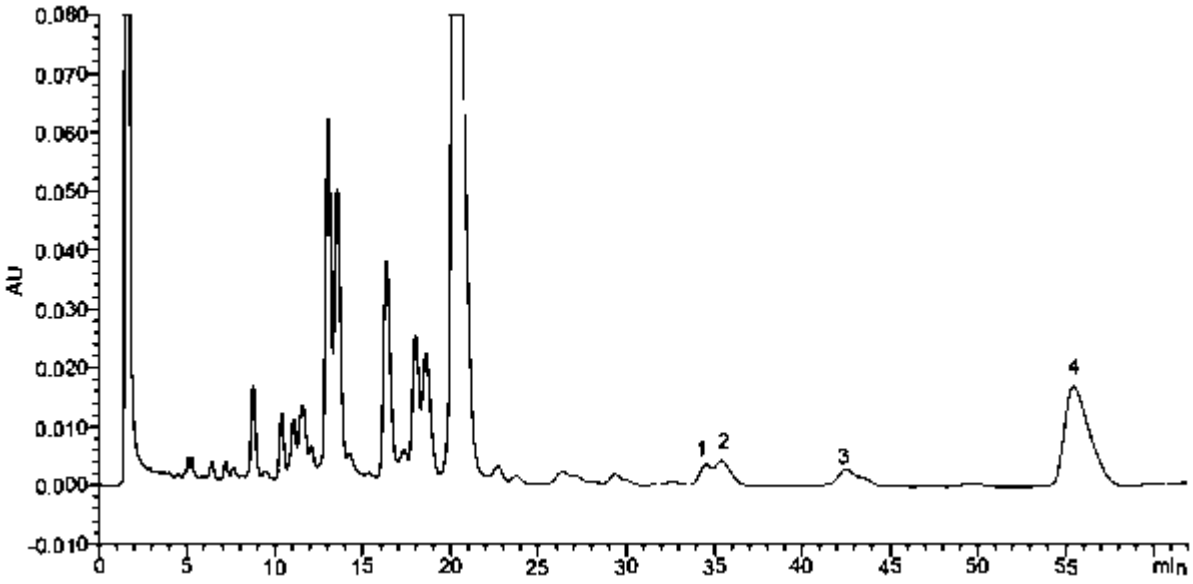
— *sum of impurities F and G*: maximum 2.0 per cent;

— *impurity H*: maximum 1.0 per cent;

— *any other impurity*: for each impurity, maximum 2.0 per cent;

— *total*: maximum 23.0 per cent;

— *reporting threshold*: 0.25 per cent.



1. impurity F 2. impurity G 3. impurity H 4. impurity E

Figure 0465.-2. – *Chromatogram for the test for related substances of bacitracin: reference solution (c)*

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa for 3 h.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 1.0 g.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *bacitracin zinc CRS* as the reference substance.

STORAGE

www.webofpharma.com

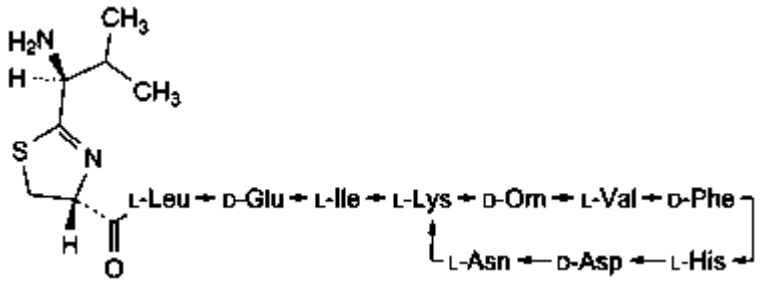
https://thuocngocanh.com/

In an airtight container at 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

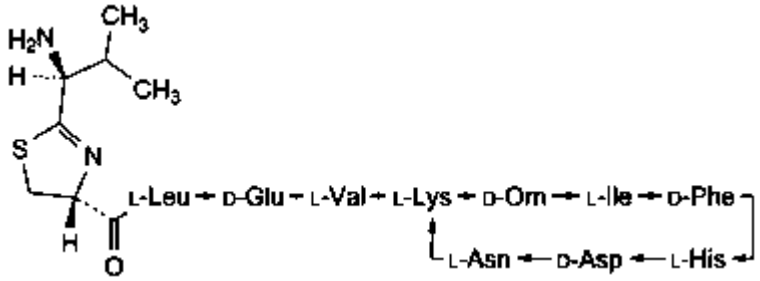
IMPURITIES

Specified impurities *A, B, C, E, F, G, H, L, M, N, O, P, Q.*

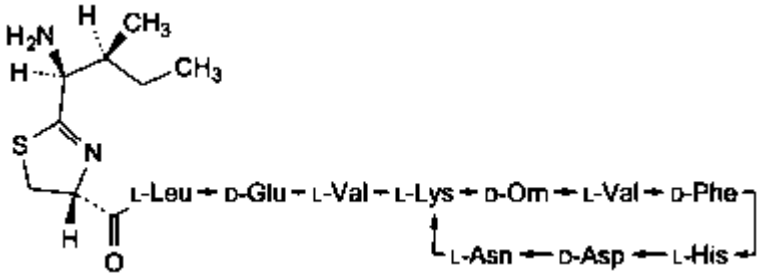
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, I, J, K.*



A. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*)-1-amino-2-methylpropyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin D1, bacitracin C2),



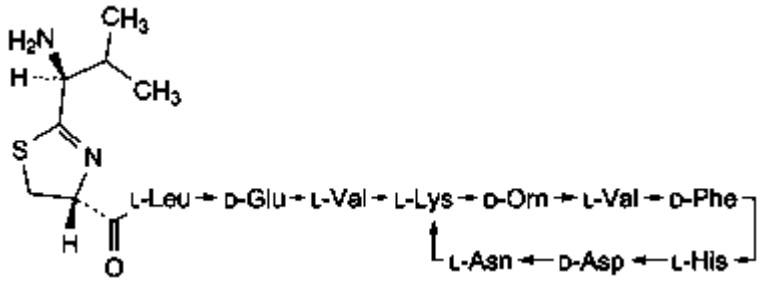
B. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*)-1-amino-2-methylpropyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin D2, bacitracin C3),



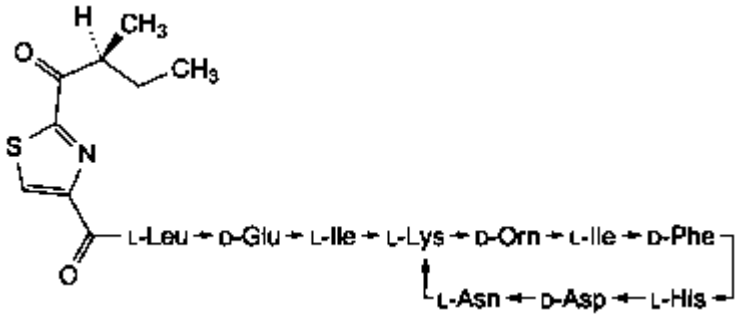
C. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin D3, bacitracin C1a),

www.webofpharma.com

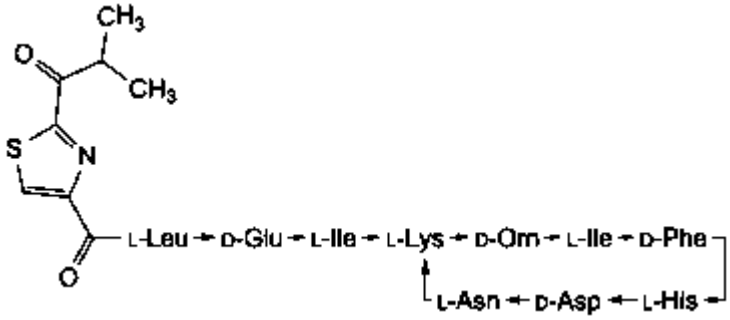
https://thuocngocanh.com/



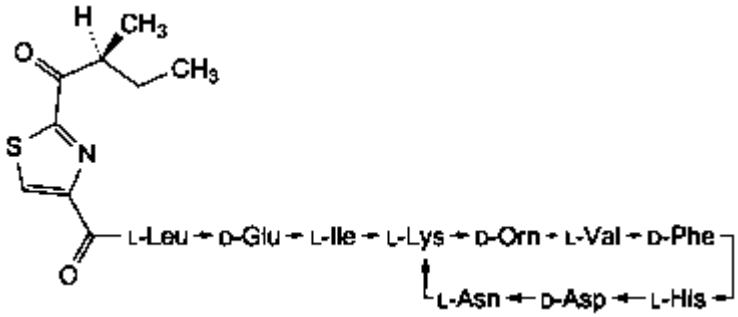
D. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*)-1-amino-2-methylpropyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin E),



E. 4,10-anhydro[*N*-[[2-[(2*S*)-2-methyl-1-oxobutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin F),



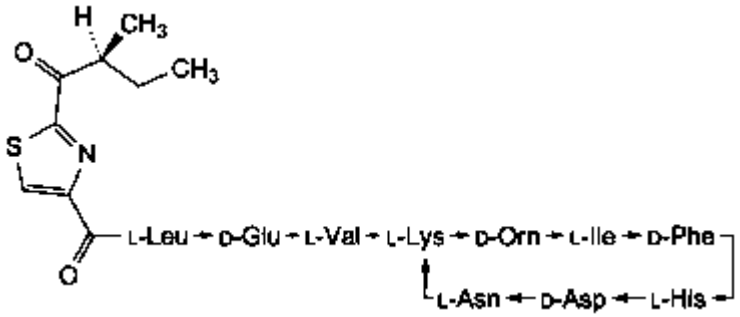
F. 4,10-anhydro[*N*-[[2-(2-methyl-1-oxopropyl)-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin H1),



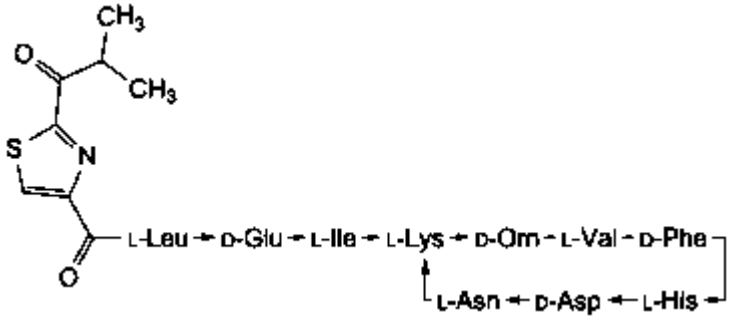
G. 4,10-anhydro[*N*-[[2-[(2*S*)-2-methyl-1-oxobutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin H2),

www.webofpharma.com

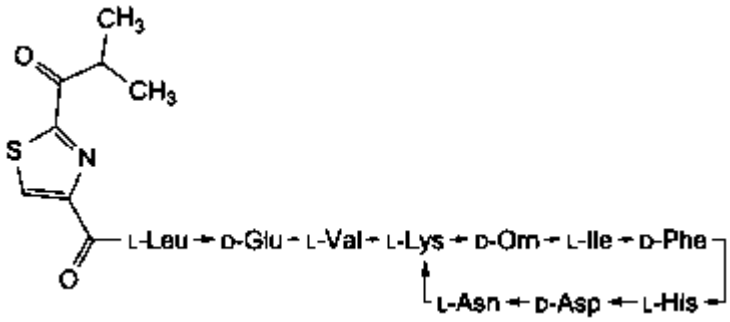
https://thuocngocanh.com/



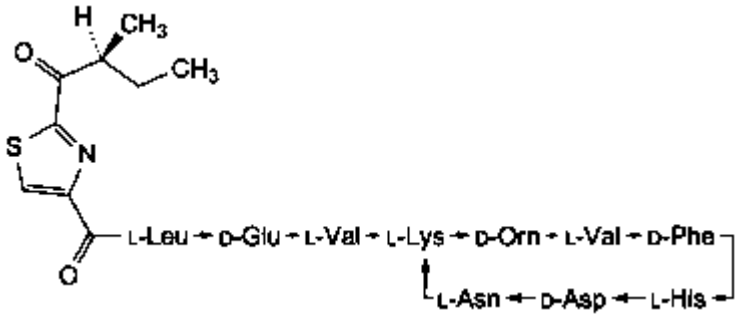
H. 4,10-anhydro[*N*-[[2-[(2*S*)-2-methyl-1-oxobutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin H3),



I. 4,10-anhydro[*N*-[[2-(2-methyl-1-oxopropyl)-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin I1),



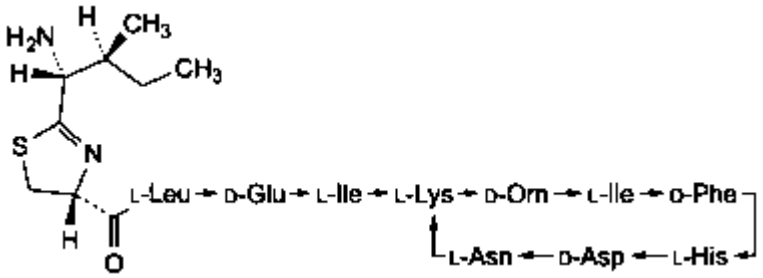
J. 4,10-anhydro[*N*-[[2-(2-methyl-1-oxopropyl)-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin I2),



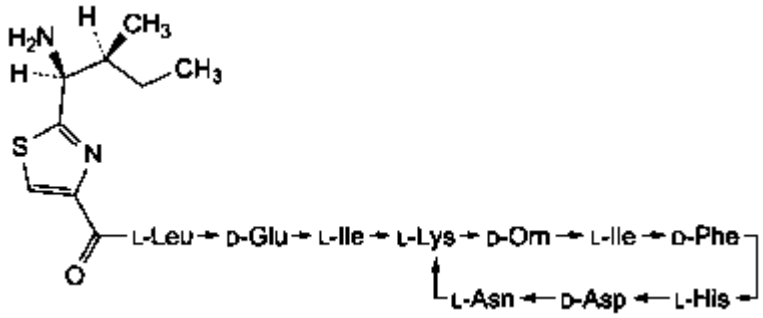
K. 4,10-anhydro[*N*-[[2-[(2*S*)-2-methyl-1-oxobutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin I3),

www.webofpharma.com

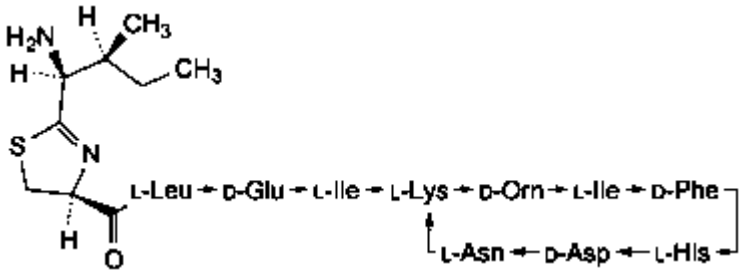
https://thuocngocanh.com/



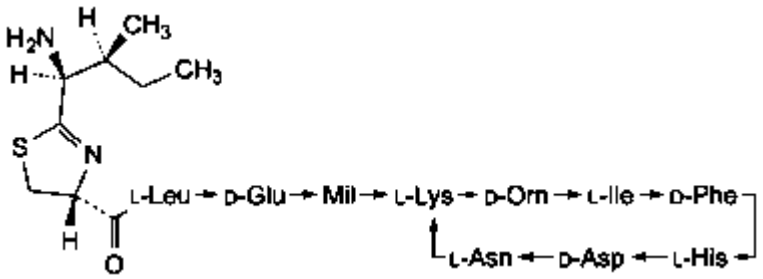
L. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*R*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin X),



M. 4,10-anhydro[*N*-[[2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin Y),



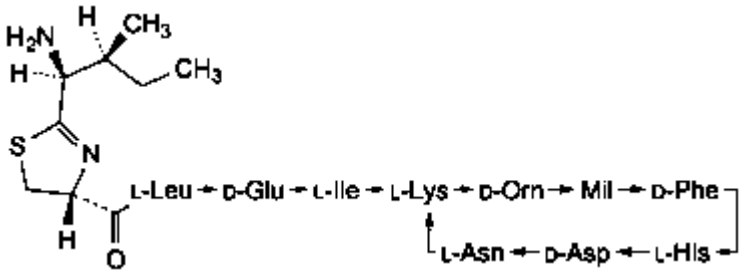
N. 4,10-anhydro[*N*-[[(4*S*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin Z),



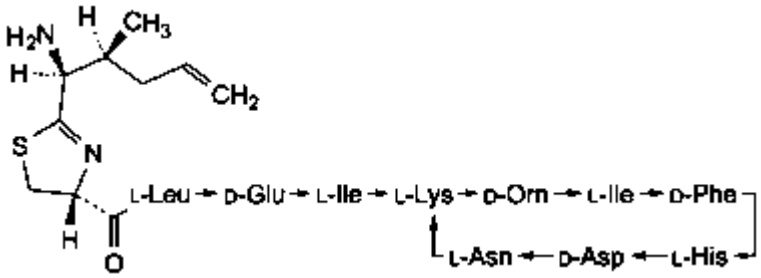
O. Mil = 5-methylene-L-isoleucine: 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-5-methylene-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin J1),

www.webofpharma.com

https://thuocngocanh.com/



P. Mil = 5-methylene-L-isoleucine: 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-5-methylene-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin J2),



Q. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylpent-4-en-1-yl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin J3).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

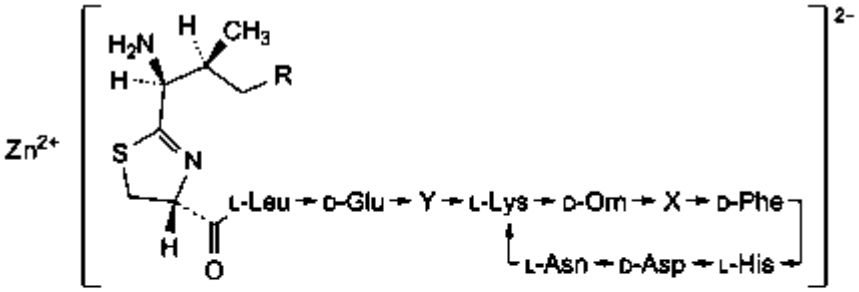
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bacitracin Zinc

General Notices

(Ph. Eur. monograph 0466)



Name	Mol. Formula	X	Y	R
Bacitracin A	$C_{66}H_{103}N_{17}O_{16}S$	L-Ile	L-Ile	CH_3
Bacitracin B1	$C_{65}H_{101}N_{17}O_{16}S$	L-Ile	L-Ile	H
Bacitracin B2	$C_{65}H_{101}N_{17}O_{16}S$	L-Val	L-Ile	CH_3
Bacitracin B3	$C_{65}H_{101}N_{17}O_{16}S$	L-Ile	L-Val	CH_3

1405-89-6

Action and use

Polypeptide antibacterial.

Preparation

Polymyxin and Bacitracin Ointment

Ph Eur

DEFINITION

Zinc complex of bacitracin, which consists of a mixture of antimicrobial polypeptides produced by certain strains of *Bacillus licheniformis* or *Bacillus subtilis*, the main components being:

— 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin A);

— 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*)-1-amino-2-methylpropyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin B1);

www.webofpharma.com

https://thuocngocanh.com/

— 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin B2);

— 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin B3).

Content

Minimum 60 IU/mg (dried substance).

CHARACTERS

Appearance

White or light yellowish-grey, hygroscopic powder.

Solubility

Slightly soluble in water and in ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, C.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 0.5 mL of *dilute hydrochloric acid R* and dilute to 1.0 mL with *water R*.

Reference solution Dissolve 10 mg of *bacitracin zinc CRS* in 0.5 mL of *dilute hydrochloric acid R* and dilute to 1.0 mL with *water R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (14:29:57 *V/V/V*).

Application 10 µL.

Development Over half of the plate.

Drying At 100-105 °C.

Detection Spray with *ninhydrin solution R1* and heat at 110 °C for 5 min.

Results The spots in the chromatogram obtained with the test solution are similar in position, size and colour to the spots in the chromatogram obtained with the reference solution.

B. Composition (see Tests).

www.webofpharma.com

https://thuocngocanh.com/

C. Ignite about 0.15 g, allow to cool and dissolve the residue in 1 mL of *dilute hydrochloric acid R*. Add 4 mL of *water R*. The solution gives the reaction of zinc (*2.3.1*).

TESTS

pH (*2.2.3*)

6.0 to 7.5.

Shake 1.0 g for about 1 min with 10 mL of *carbon dioxide-free water R* and filter.

Composition

Liquid chromatography (*2.2.29*): use the normalisation procedure. *Prepare the solutions immediately before use.*

Solution A 40 g/L solution of *sodium edetate R* adjusted to pH 7.0 with *dilute sodium hydroxide solution R*.

Solution B In a volumetric flask, dissolve 54.4 g of *potassium dihydrogen phosphate R* in *water for chromatography R* and dilute to 2000 mL with the same solvent. Adjust to pH 6.0 with a 34.8 g/L solution of *dipotassium hydrogen phosphate R* and filter through a membrane filter (nominal pore size 0.45 µm).

Test solution Dissolve 0.100 g of the substance to be examined in solution A and dilute to 50.0 mL with the same solution.

Reference solution (a) Dissolve 20.0 mg of *bacitracin for system suitability CRS* in solution A and dilute to 10.0 mL with the same solution.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (c) In order to prepare impurities E, F, G and H *in situ*, heat about 4 mL of reference solution (a) in a water-bath for 30 min. Cool to room temperature.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 28 ± 2 °C.

Mobile phase *acetonitrile R*, solution B, *water for chromatography R*, *methanol R* (43:100:300:557 *V/V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 100 µL of the test solution and reference solutions (a) and (b).

Run time 3 times the retention time of bacitracin A.

www.webofpharma.com

https://thuocngocanh.com/

Identification of peaks Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurity M and bacitracins A, B1, B2 and B3 (see Figure 0466.-1).

Relative retention With reference to bacitracin A (retention time = about 20 min): impurity A = about 0.44; impurity B = about 0.52; impurity C = about 0.55; bacitracin B1 = about 0.65; bacitracin B2 = about 0.67; bacitracin B3 = about 0.81; impurity M = about 0.87; impurity N = about 0.90; impurity L = about 0.93; impurity O = about 1.2; impurities P and Q = about 1.3; impurity F = about 1.6; impurity G = about 1.8; impurity H = about 2.1; impurity E = about 2.8.

If necessary, adjust the composition of the mobile phase by changing the amount of organic modifier whilst keeping the ratio constant between methanol and acetonitrile.

System suitability:

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of the peak due to bacitracin B2 and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to bacitracin B1 in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.1, where H_p = height above the baseline of the peak due to impurity M and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to bacitracin B3 in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 50 for the peak due to bacitracin A in the chromatogram obtained with reference solution (b).

Limits:

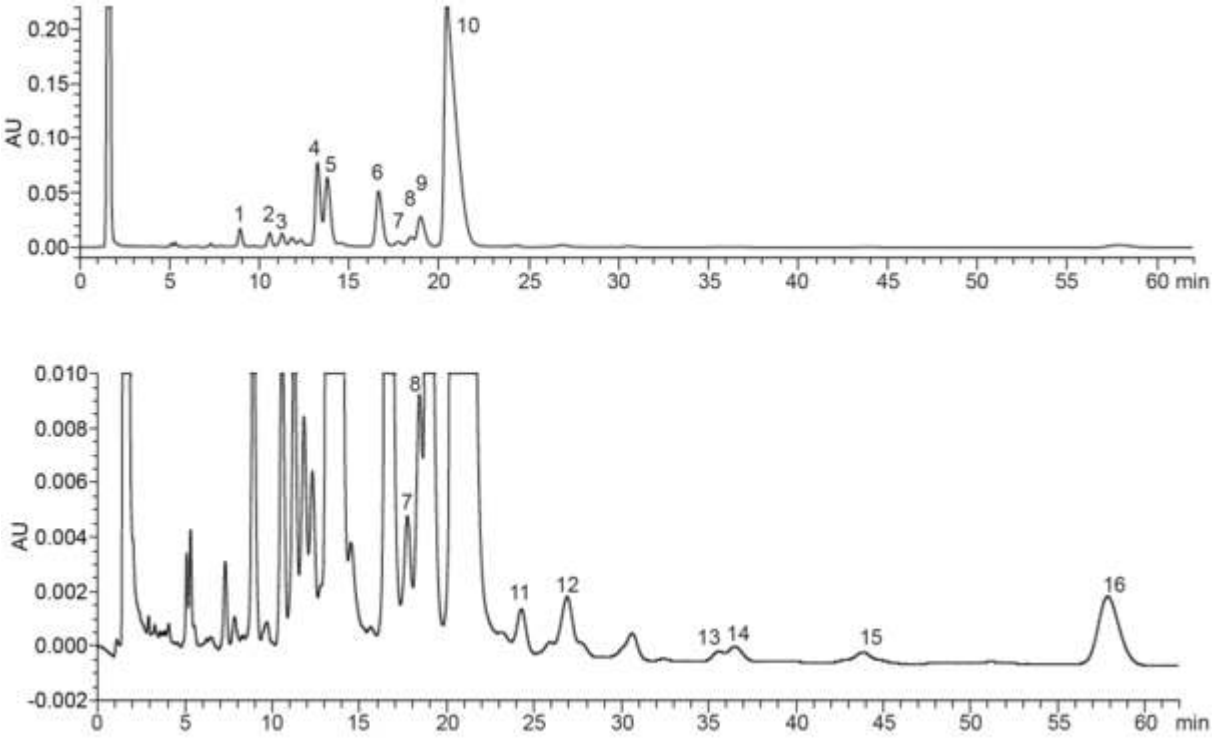
— *bacitracin A*: minimum 45.0 per cent;

— *sum of bacitracins A, B1, B2 and B3*: minimum 77.0 per cent;

— *reporting threshold*: 0.25 per cent.

www.webofpharma.com

https://thuocngocanh.com/



1. impurity A	5. bacitracin B2	9. impurity L	13. impurity F
2. impurity B	6. bacitracin B3	10. bacitracin A	14. impurity G
3. impurity C	7. impurity M	11. impurity O	15. impurity H
4. bacitracin B1	8. impurity N	12. impurities P and Q	16. impurity E

Figure 0466.-1. – *Chromatogram for the test for composition of bacitracin zinc: test solution*

Related substances

Liquid chromatography (2.2.29) as described in the test for composition with the following modifications. Use the normalisation procedure.

Injection Test solution and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, L, M, N, O, P and Q (see Figure 0466.-1); use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities E, F, G, and H (see Figure 0466.-2).

Limits:

— *sum of impurities L and N*: maximum 8.0 per cent;

— *impurity E*: maximum 4.0 per cent;

— *impurity A*: maximum 3.5 per cent;

— *impurities B, M*: for each impurity, maximum 3.0 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *impurity C*: maximum 2.5 per cent;

— *sum of impurities O, P and Q*: maximum 2.5 per cent;

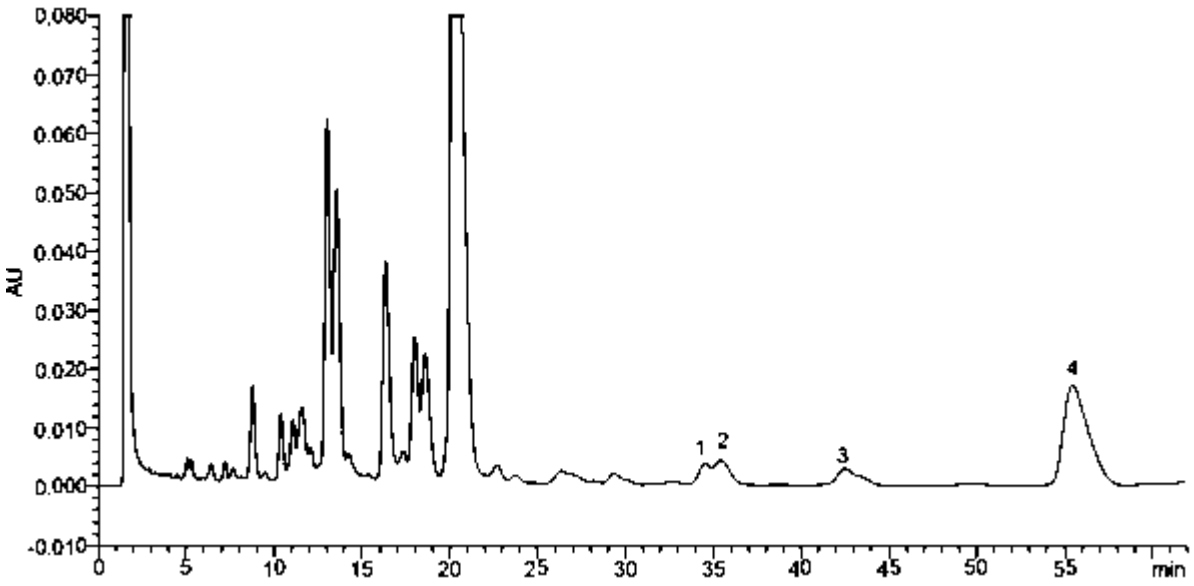
— *sum of impurities F and G*: maximum 2.0 per cent;

— *impurity H*: maximum 1.0 per cent;

— *any other impurity*: for each impurity, maximum 2.0 per cent;

— *total*: maximum 23.0 per cent;

— *reporting threshold*: 0.25 per cent.



1. impurity F 2. impurity G 3. impurity H 4. impurity E

Figure 0466.-2. – *Chromatogram for the test for related substances of bacitracin zinc: reference solution (c)*

Zinc

3.5 per cent to 5.5 per cent (dried substance).

Dissolve 0.200 g in a mixture of 2.5 mL of *dilute acetic acid R* and 2.5 mL of water. Add 50 mL of *water R*, 50 mg of *xylenol orange triturate R* and sufficient *hexamethylenetetramine R* to produce a red colour. Add 2 g of *hexamethylenetetramine R* in excess. Titrate with *0.01 M sodium edetate* until a yellow colour is obtained.

1 mL of *0.01 M sodium edetate* is equivalent to 0.654 mg of Zn.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa for 3 h.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Suspend 50.0 mg in 5 mL of *water R*, add 0.5 mL of *dilute hydrochloric acid R* and dilute to 100.0 mL with *water R*. Allow the solution to stand for 30 min. Carry out the microbiological assay of antibiotics (2.7.2). Use *bacitracin zinc CRS* as the chemical reference substance.

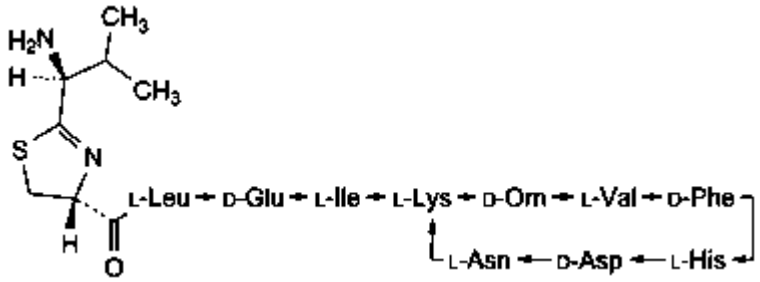
STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

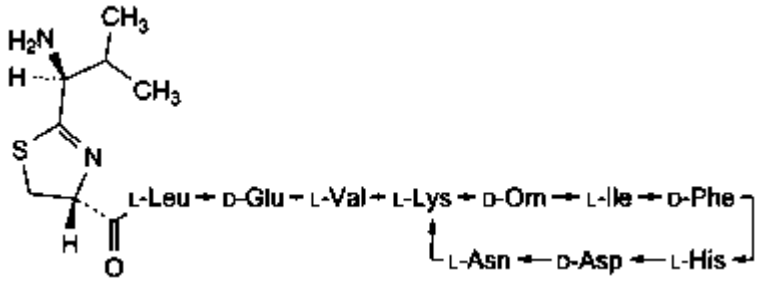
IMPURITIES

Specified impurities *A, B, C, E, F, G, H, L, M, N, O, P, Q.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, I, J, K.*



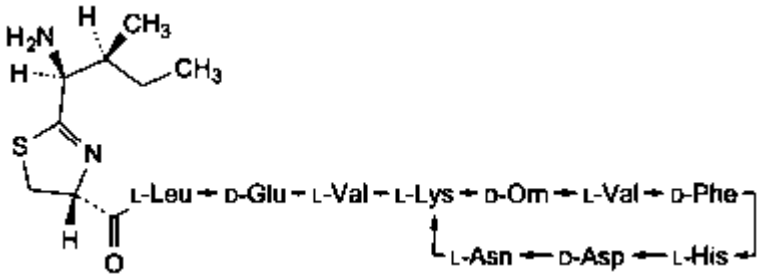
A. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*)-1-amino-2-methylpropyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin D1, bacitracin C2),



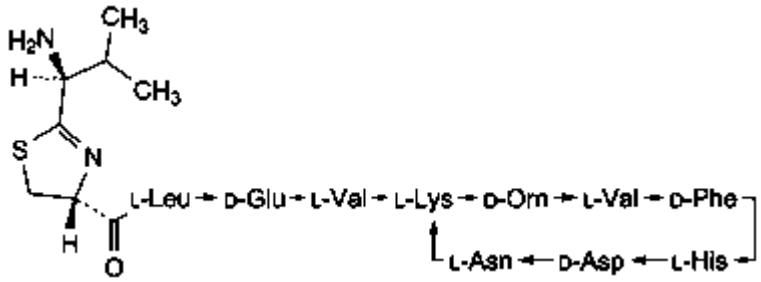
B. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*)-1-amino-2-methylpropyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin D2, bacitracin C3),

www.webofpharma.com

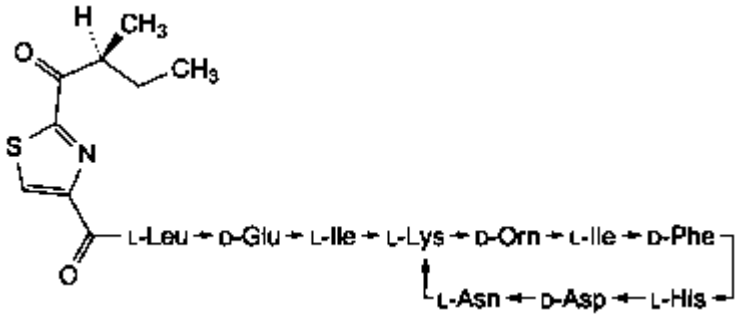
https://thuocngocanh.com/



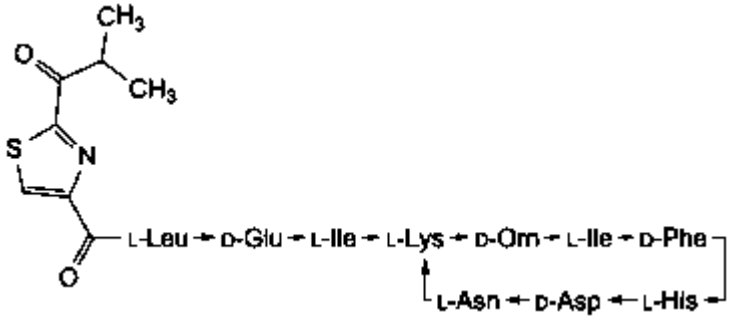
C. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin D3, bacitracin C1a),



D. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*)-1-amino-2-methylpropyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin E),



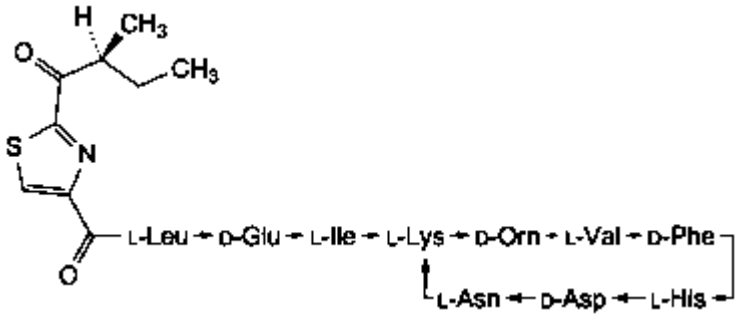
E. 4,10-anhydro[*N*-[[2-[(2*S*)-2-methyl-1-oxobutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine], (bacitracin F),



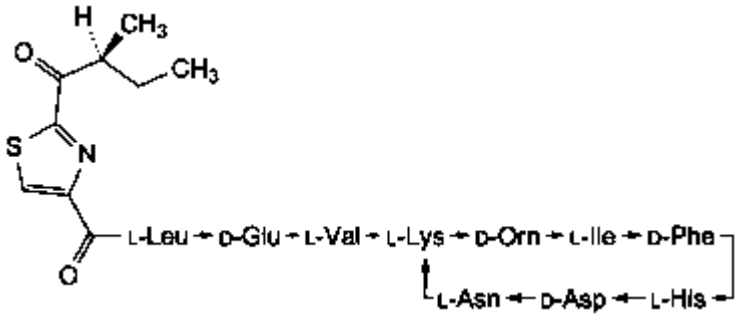
F. 4,10-anhydro[*N*-[[2-(2-methyl-1-oxopropyl)-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin H1),

www.webofpharma.com

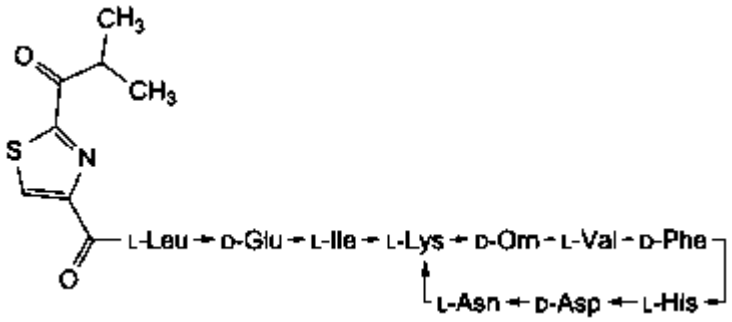
https://thuocngocanh.com/



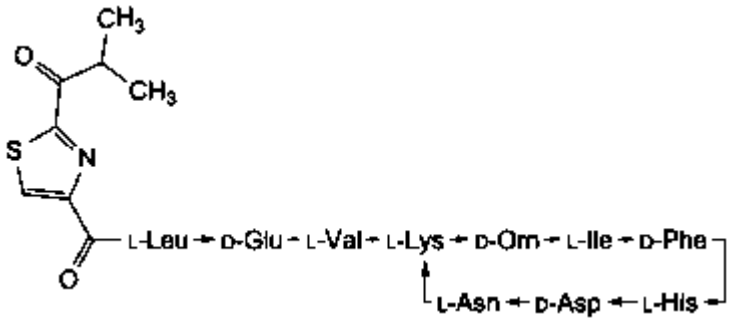
G. 4,10-anhydro[*N*-[[2-[(2*S*)-2-methyl-1-oxobutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin H2),



H. 4,10-anhydro[*N*-[[2-[(2*S*)-2-methyl-1-oxobutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin H3),



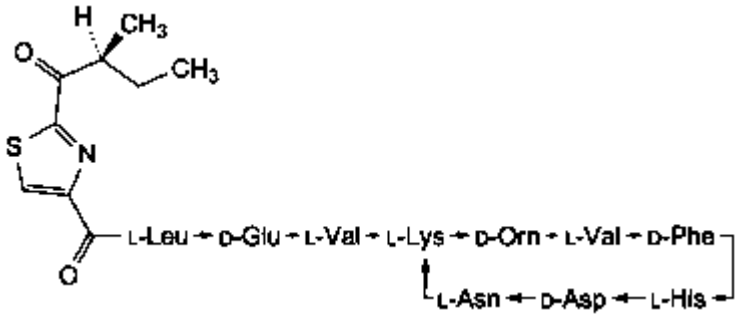
I. 4,10-anhydro[*N*-[[2-(2-methyl-1-oxopropyl)-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin I1),



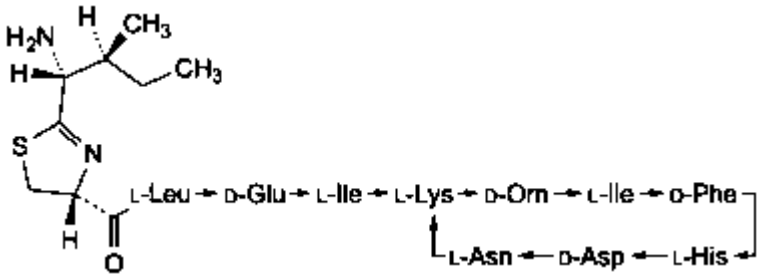
J. 4,10-anhydro[*N*-[[2-(2-methyl-1-oxopropyl)-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin I2),

www.webofpharma.com

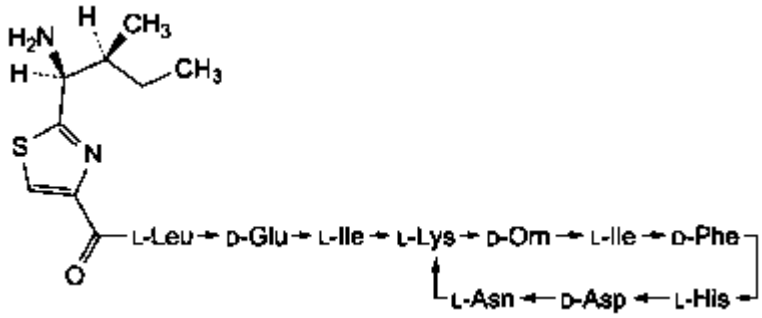
https://thuocngocanh.com/



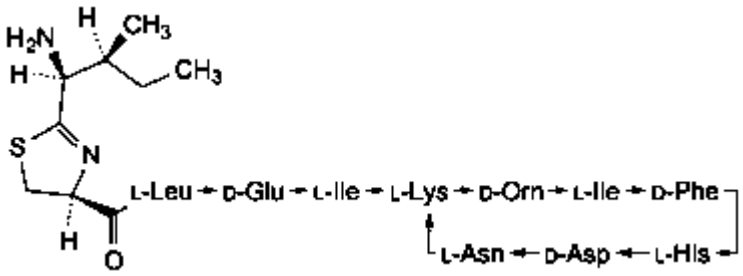
K. 4,10-anhydro[*N*-[[2-[(2*S*)-2-methyl-1-oxobutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-valyl-L-lysyl-D-ornithyl-L-valyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin I3),



L. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*R*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin X),



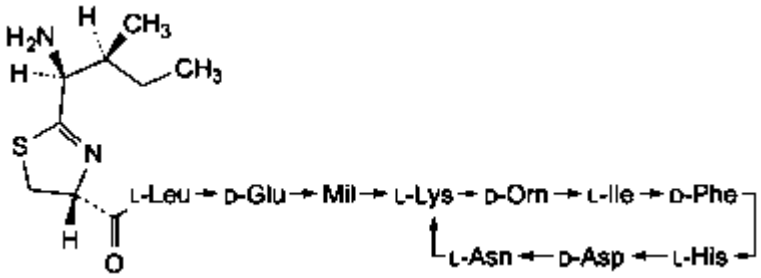
M. 4,10-anhydro[*N*-[[2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin Y),



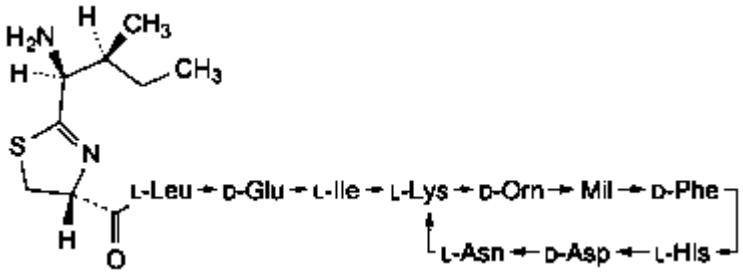
N. 4,10-anhydro[*N*-[[(4*S*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin Z),

www.webofpharma.com

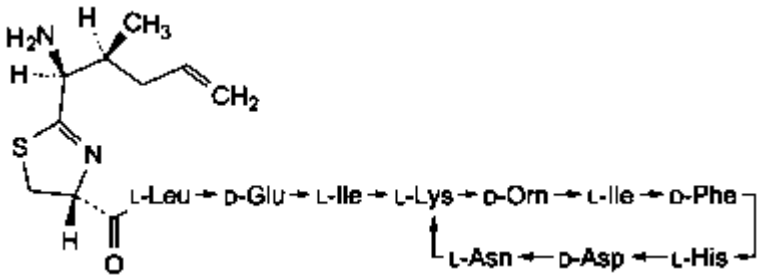
https://thuocngocanh.com/



O. Mil = 5-methylene-L-isoleucine: 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-5-methylene-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin J1),



P. Mil = 5-methylene-L-isoleucine: 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylbutyl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-5-methylene-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin J2),



Q. 4,10-anhydro[*N*-[[(4*R*)-2-[(1*S*,2*S*)-1-amino-2-methylpent-4-en-1-yl]-4,5-dihydro-1,3-thiazol-4-yl]carbonyl]-L-leucyl-D-α-glutamyl-L-isoleucyl-L-lysyl-D-ornithyl-L-isoleucyl-D-phenylalanyl-L-histidyl-D-α-aspartyl-L-asparagine] (bacitracin J3).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

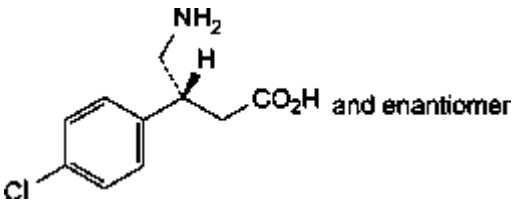
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Baclofen

General Notices

(Ph. Eur. monograph 0653)



$C_{10}H_{12}ClNO_2$ 213.7 *1134-47-0*

Action and use

Skeletal muscle relaxant.

Preparations

Baclofen Oral Solution

Baclofen Tablets

Ph Eur

DEFINITION

(3*RS*)-4-Amino-3-(4-chlorophenyl)butanoic acid.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 70 mg in *water R* and dilute to 100.0 mL with the same solvent.

Spectral range 220-320 nm.

Absorption maxima At 259 nm, 266 nm and 275 nm.

Resolution (2.2.25): minimum 1.5 for the absorbance ratio.

Specific absorbance at the absorption maxima:

— at 259 nm: 9.8 to 10.8;

— at 266 nm: 11.5 to 12.7;

— at 275 nm: 8.4 to 9.3.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs prepared using 3 mg of substance and 300 mg of *potassium bromide R*.

Comparison *baclofen CRS*.

If the spectra obtained in the solid state show differences, dissolve 0.1 g of each of the substances separately in 1 mL of *dilute sodium hydroxide solution R* and add 10 mL of *ethanol (96 per cent) R* and 1 mL of *dilute acetic acid R*. Allow to stand for 1 h. Filter, wash the precipitate with *ethanol (96 per cent) R* and dry *in vacuo*. Prepare new discs and record the spectra.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution Dissolve 10 mg of *baclofen CRS* in the mobile phase and dilute to 10 mL with the mobile phase.

Plate *TLC silica gel G plate R*.

Mobile phase *anhydrous formic acid R*, *water R*, *methanol R*, *chloroform R*, *ethyl acetate R* (5:5:20:30:40 *V/V/V/V/V*).

Application 5 µL.

Development Over a path of 12 cm.

www.webofpharma.com

https://thuocngocanh.com/

Drying Allow the solvents to evaporate.

Detection Spray with *ninhydrin solution R3* until the plate is slightly wet. Place in an oven maintained at 100 °C for 10 min. Examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 0.50 g in *1 M sodium hydroxide* and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *baclofen impurity A CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (d) Dilute 2.0 mL of the test solution and 2.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase Dissolve 1.822 g of *sodium hexanesulfonate R* in 1 L of a mixture of 560 volumes of *water R*, 440 volumes of *methanol R* and 5 volumes of *glacial acetic acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 266 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 5 times the retention time of baclofen.

System suitability Reference solution (d):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 2.0 between the peaks due to baclofen and impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

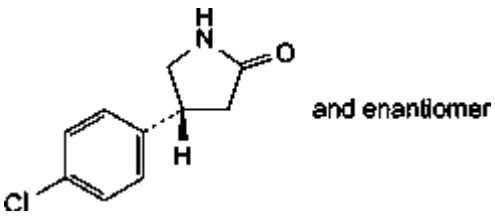
Dissolve 0.1500 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 21.37 mg of $C_{10}H_{12}ClNO_2$.

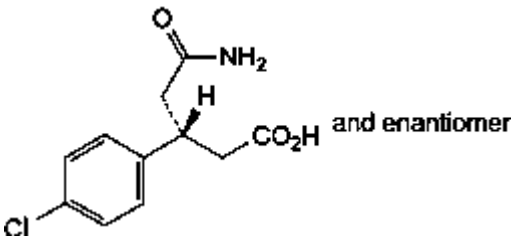
IMPURITIES

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. (4*R*S)-4-(4-chlorophenyl)pyrrolidin-2-one,



B. (3*RS*)-5-amino-3-(4-chlorophenyl)-5-oxopentanoic acid.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Baclofen Oral Solution

General Notices

Action and use

Skeletal muscle relaxant.

DEFINITION

Baclofen Oral Solution is a solution of Baclofen in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of baclofen, $C_{10}H_{12}ClNO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of 35 volumes of *acetonitrile* and 65 volumes of *water*.

(1) Dilute a volume of the oral solution containing 5 mg of Baclofen to 100 mL.

(2) 0.005% w/v of *baclofen BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air.

(f) Place an evaporating dish containing 4 mL of *water*, 1 mL of 7M *hydrochloric acid* and 0.5 g of *potassium permanganate* in a chromatography tank, close the tank and allow to stand for 2 minutes. Place the plate in the tank, close the tank and leave the plate in contact with the vapour for 1 minute.

(g) After removal of the plate, place it in a current of cold air until an area of coating below the line of application shows only a faint blue colour on the addition of 0.05 mL of *potassium iodide and starch solution*. Spray the plate with *potassium iodide and starch solution* and examine in daylight.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *water* and 80 volumes of *butan-1-ol*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Impurity A

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the oral solution containing 5 mg of Baclofen to 50 mL.
(2) 0.0002% w/v of *baclofen impurity A EPCRS*.
(3) 0.01% w/v of *baclofen BPCRS*, 0.0003% w/v of *propyl 4-hydroxybenzoate*, 0.0003% w/v of *methyl 4-hydroxybenzoate* and 0.0002% w/v of *baclofen impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

MOBILE PHASE

5 g of *sodium dodecyl sulfate* in a mixture of 5 mL of *orthophosphoric acid* and 650 mL of *water* and diluted to 1000 mL with *acetonitrile R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methyl-4-hydroxybenzoate and impurity A (lactam) and between the peaks due to impurity A and propyl-4-hydroxybenzoate is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the oral solution containing 5 mg of Baclofen to 50 mL.
(2) 0.01% w/v of *baclofen BPCRS*.
(3) 0.01% w/v of *baclofen BPCRS*, 0.0003% w/v of *propyl 4-hydroxybenzoate* and 0.0002% w/v of *baclofen impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 218 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 g of *sodium dodecyl sulfate* in a mixture of 5 mL of *orthophosphoric acid* and 650 mL of *water* and diluting to 1000 mL with *acetonitrile R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and propyl-4-hydroxybenzoate is at least 5.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{10}H_{12}ClNO_2$, weight in volume, using the declared content of $C_{10}H_{12}ClNO_2$ in *baclofen BPCRS*.

STORAGE

Baclofen Oral Solution should be stored below 25° and protected from light. It should not be refrigerated.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Baclofen Tablets

General Notices

Action and use

Skeletal muscle relaxant.

DEFINITION

Baclofen Tablets contain Baclofen.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of baclofen, $C_{10}H_{12}ClNO_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Baclofen with 20 mL of a mixture of 4 volumes of *absolute ethanol* and 1 volume of *glacial acetic acid* for 30 minutes and filter.

(2) 0.1% w/v of *baclofen BPCRS* in a mixture of 4 volumes of *absolute ethanol* and 1 volume of *glacial acetic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution* and heat at 100° for 10 minutes.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *water* and 80 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 20 mL sample of the medium and filter through a membrane filter with a nominal pore size not greater than 0.45 µm, discarding the first 10 mL of filtrate.

(2) 0.001% w/v of *baclofen BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

DETERMINATION OF CONTENT

Calculate the total content of baclofen, $C_{10}H_{12}ClNO_2$, in the medium from the declared content of $C_{10}H_{12}ClNO_2$ in *baclofen BPCRS*.

Impurity A

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Baclofen with 50 mL for 30 minutes, shaking occasionally to disperse the sample, and filter through a glass-fibre filter (Whatman GF/C is suitable).

(2) 0.004% w/v of *baclofen impurity A EPCRS*.

(3) 0.2% w/v of *baclofen BPCRS* and 0.004% w/v of *baclofen impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 266 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *glacial acetic acid*, 440 volumes of *methanol* and 560 volumes of *water*, the mixture containing 0.182% w/v of *sodium hexanesulfonate*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to baclofen and impurity A is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to baclofen impurity A is not greater than the area of the peak in the chromatogram obtained with solution (2) (2%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add a quantity of whole tablets containing 0.1 g of Baclofen to 25 mL of a mixture of 1 volume of *glacial acetic acid* and 100 volumes of *water* and disperse with the aid of ultrasound. Dilute to 50 mL with *methanol*, filter and use the filtrate.
(2) 0.2% w/v of *baclofen BPCRS* in a mixture of 1 volume of *glacial acetic acid*, 100 volumes of *methanol* and 100 volumes of *water*.
(3) 0.2% w/v of *baclofen BPCRS* and 0.004% w/v of *baclofen impurity A EPCRS* in a mixture of 1 volume of *glacial acetic acid*, 100 volumes of *methanol* and 100 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 265 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.01M *sodium hexanesulfonate* in a mixture of 1 volume of *glacial acetic acid*, 100 volumes of *methanol* and 100 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to baclofen and impurity A is at least 7.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{12}ClNO_2$ in the tablets using the declared content of $C_{10}H_{12}ClNO_2$ in *baclofen BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

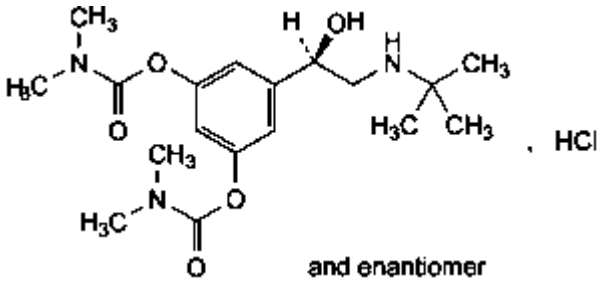
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bambuterol Hydrochloride

General Notices

(Ph. Eur. monograph 1293)



$C_{18}H_{30}ClN_3O_5$ 403.9 *81732-46-9*

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

Ph Eur

DEFINITION

5-[(1*RS*)-2-(*tert*-Butylamino)-1-hydroxyethyl]-1,3-phenylene bis(dimethylcarbamate) hydrochloride.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *bambuterol hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in a mixture of 1 volume of *water R* and 6 volumes of *acetone R*, cool in ice to precipitate and dry both precipitates *in vacuo* at 50 °C to constant weight. Record new spectra using the residues.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 4.0 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M hydrochloric acid*. The solution is red. Add 0.4 mL of *0.01 M sodium hydroxide*. The solution is yellow.

Optical rotation (*2.2.7*)

-0.10° to + 0.10°.

Dilute 1 mL of solution S to 10 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

0.050 M phosphate buffer solution Dissolve 6.90 g of *sodium dihydrogen phosphate monohydrate R* in *water for chromatography R*, adjust to pH 3.0 with a 50 g/L solution of *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 5.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *bambuterol impurity mixture CRS* (impurities C and D) in 1 mL of the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 1.3 g of *sodium octanesulfonate R* in 430 mL of a mixture of 25 volumes of *acetonitrile R1* and 75 volumes of *methanol R2*, then mix the solution with 570 mL of the 0.050 M phosphate buffer solution.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL; inject the mobile phase as a blank.

Run time 1.5 times the retention time of bambuterol.

Identification of impurities Use the chromatogram supplied with *bambuterol impurity mixture CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and D.

Relative retention With reference to bambuterol (retention time = about 9 min): impurity C = about 0.45; impurity D = about 0.50.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities C and D.

Calculation of percentage contents:

— for each impurity, use the concentration of bambuterol hydrochloride in reference solution (b).

Limits:

— *impurity C*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.320 g in 50 mL of *ethanol (96 per cent) R* and add 5 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 40.39 mg of $C_{18}H_{30}ClN_3O_5$.

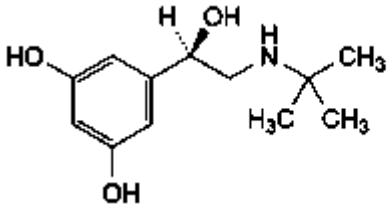
IMPURITIES

Specified impurities *C*.

www.webofpharma.com

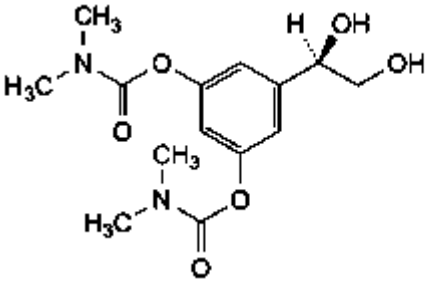
https://thuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, D, E, F.*



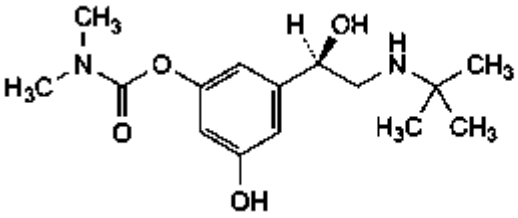
and enantiomer

A. 5-[(1*RS*)-2-(*tert*-butylamino)-1-hydroxyethyl]benzene-1,3-diol (terbutaline),



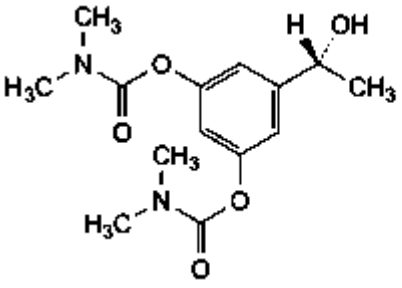
and enantiomer

B. 5-[(1*RS*)-1,2-dihydroxyethyl]-1,3-phenylene bis(dimethylcarbamate),



and enantiomer

C. 3-[(1*RS*)-2-(*tert*-butylamino)-1-hydroxyethyl]-5-hydroxyphenyl dimethylcarbamate,

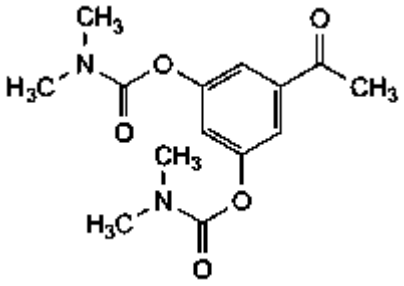


and enantiomer

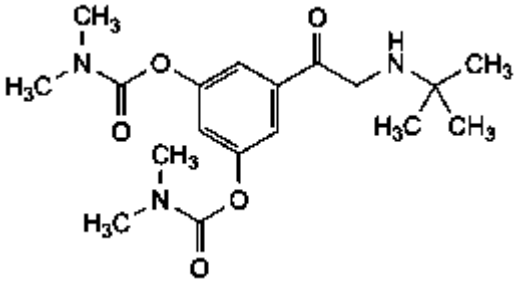
D. 5-[(1*RS*)-1-hydroxyethyl]-1,3-phenylene bis(dimethylcarbamate),

www.webofpharma.com

https://thuocngocanh.com/



E. 5-acetyl-1,3-phenylene bis(dimethylcarbamate),



F. 5-[(*tert*-butylamino)acetyl]-1,3-phenylene bis(dimethylcarbamate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Barium Sulfate

General Notices

(Ph. Eur. monograph 0010)

$BaSO_4$ 233.4 *7727-43-7*

Action and use

Radio-opaque substance used in the investigation of the gastro-intestinal tract.

Preparation

Barium Sulfate for Suspension

Ph Eur

CHARACTERS

Appearance

Fine, white or almost white powder, free from gritty particles.

Solubility

Practically insoluble in water and in organic solvents. It is very slightly soluble in acids and in solutions of alkali hydroxides.

IDENTIFICATION

A. Boil a suspension of 0.2 g with 5 mL of a 500 g/L solution of *sodium carbonate R* for 5 min, add 10 mL of *water R*, filter and acidify a part of the filtrate with *dilute hydrochloric acid R*. The solution gives the reactions of sulfates (*2.3.1*).

B. Wash the residue collected in the preceding test with 3 successive small quantities of *water R*. To the residue add 5 mL of *dilute hydrochloric acid R*, filter and add to the filtrate 0.3 mL of *dilute sulfuric acid R*. A white precipitate is formed that is insoluble in *dilute sodium hydroxide solution R*.

TESTS

Solution S

To 20.0 g add 40 mL of *distilled water R* and 60 mL of *dilute acetic acid R*. Boil for 5 min, filter and dilute the cooled filtrate to 100 mL with *distilled water R*.

Acidity or alkalinity

www.webofpharma.com

https://thietbiuocngocanh.com/

Heat 5.0 g with 20 mL of *carbon dioxide-free water R* on a water-bath for 5 min and filter. To 10 mL of the filtrate add 0.05 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Acid-soluble substances

Maximum 0.3 per cent.

Evaporate 25 mL of solution S to dryness on a water-bath and dry to constant mass at 100-105 °C. The residue weighs a maximum of 15 mg.

Oxidisable sulfur compounds

Shake 1.0 g with 5 mL of *water R* for 30 s and filter. To the filtrate add 0.1 mL of *starch solution R*, dissolve 0.1 g of *potassium iodide R* in the mixture, add 1.0 mL of a freshly prepared 3.6 mg/L solution of *potassium iodate R* and 1 mL of *1 M hydrochloric acid* and shake well. The colour of the solution is more intense than that of a standard prepared at the same time and in the same manner, but omitting the potassium iodate.

Soluble barium salts

Maximum 10 ppm.

To 2.5 mL of a 0.2 mg/L solution of *barium nitrate R* in a mixture of 30 volumes of *ethanol (96 per cent) R* and 70 volumes of *water R*, add 10 mL of *dilute sulfuric acid R*. Shake and allow to stand for 5 min. To 1 mL of this solution add 10 mL of solution S. Prepare a standard in the same manner using 10 mL of *barium standard solution (2 ppm Ba) R* instead of solution S.

After 10 min, any opalescence in the test solution is not more intense than that in the standard.

Loss on ignition

Maximum 2.0 per cent, determined on 1.0 g at 600 ± 50 °C.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Barium Sulfate for Suspension

General Notices

Barium Sulphate for Suspension

Action and use

Radio-opaque preparation used in the investigation of the gastro-intestinal tract.

Preparation

Barium Sulfate Oral Suspension

DEFINITION

Barium Sulfate for Suspension is a dry mixture of Barium Sulfate with a suitable dispersing agent and may contain suitable flavours and suitable antimicrobial preservatives.

Content of barium sulfate, $BaSO_4$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A fine, white or creamy white powder.

IDENTIFICATION

A. Ignite 1 g to constant weight. To 0.2 g of the residue add 5 mL of a 50% w/v solution of *sodium carbonate* and boil for 5 minutes. Add 10 mL of *water* and filter. Reserve the residue for test B. Acidify a portion of the filtrate with 2M *hydrochloric acid*. The solution yields the reactions characteristic of *sulfates*, Appendix VI.

B. Wash the residue reserved in test A with *water*, add 5 mL of *2M hydrochloric acid*, mix well and filter. Add 0.3 mL of *1M sulfuric acid* to the filtrate. A white precipitate is produced which is insoluble in 2M *hydrochloric acid*.

TESTS

Acidity or alkalinity

pH of an aqueous suspension containing the equivalent of 60% w/w of Barium Sulfate or, for lower strengths, the aqueous suspension at the strength of intended use, 3.5 to 8.5, Appendix V L.

Loss on drying

www.webofpharma.com

https://thuocngocanh.com/

When dried at 105° for 4 hours, loses not more than 1.0% of its weight. Use 1 g.

ASSAY

To a quantity containing 0.6 g of Barium Sulfate in a platinum dish add 5 g of *sodium carbonate* and 5 g of *potassium carbonate sesquihydrate* and mix. Heat to 1000° and maintain at this temperature for 15 minutes. Allow to cool and suspend the residue in 150 mL of *water*. Wash the dish with 2 mL of *6M acetic acid* and add the washings to the suspension. Cool in ice and decant the supernatant liquid, transferring as little of the solid matter as possible to the filter. Wash the residue with successive quantities of a 2% w/v solution of *sodium carbonate* until the washings are free from sulfate and discard the washings. Add 5 mL of *2M hydrochloric acid* to the filter, wash through into the vessel containing the bulk of the solid matter with *water*, add 5 mL of *hydrochloric acid* and dilute to 100 mL with *water*. Add 10 mL of a 40% w/v solution of *ammonium acetate*, 25 mL of a 10% w/v solution of *potassium dichromate* and 10 g of *urea*. Cover and digest in a hot-air oven at 80° to 85° for 16 hours. Filter whilst still hot through a sintered-glass filter (ISO 4793, porosity grade 4, is suitable), washing the precipitate initially with a 0.5% w/v solution of *potassium dichromate* and finally with 2 mL of *water*. Dry to constant weight at 105°. Each g of the residue is equivalent to 0.9213 g of barium sulfate, $BaSO_4$.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Barium Sulfate Oral Suspension

General Notices

Barium Sulphate Oral Suspension

DEFINITION

Barium Sulfate Oral Suspension is a suspension of Barium Sulfate for Suspension in a suitable aqueous vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of barium sulfate, $BaSO_4$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A smooth, white or creamy white suspension.

IDENTIFICATION

Evaporate 1 mL to dryness and ignite to constant weight. The residue complies with the following tests.

A. To 0.2 g add 5 mL of a 50% w/v solution of *sodium carbonate* and boil for 5 minutes, add 10 mL of *water* and filter. Reserve the residue for test B. Acidify the filtrate with 2M *hydrochloric acid*. The resulting solution yields the reactions characteristic of *sulfates*, Appendix VI.

B. Wash the residue reserved in test A with *water*, add 5 mL of 2M *hydrochloric acid*, mix well and filter. Add 0.3 mL of 1M *sulfuric acid* to the filtrate. A white precipitate is produced which is insoluble in 2M *hydrochloric acid*.

Acidity or alkalinity

pH, 3.5 to 8.5, Appendix V L.

ASSAY

Evaporate to dryness a quantity containing 0.6 g of Barium Sulfate in a platinum dish on a water bath and carry out the Assay described under Barium Sulfate for Suspension, beginning at the words ‘add 5 g of *sodium carbonate*…’. Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the percentage of $BaSO_4$, weight in volume.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Basic Butylated Methacrylate Copolymer

General Notices

(Ph. Eur. monograph 1975)

Action and use

Excipient.

Ph Eur

DEFINITION

Copolymer of 2-(dimethylamino)ethyl methacrylate, butyl methacrylate and methyl methacrylate having a mean relative molecular mass of about 47 000. The ratio of 2-(dimethylamino)ethyl methacrylate groups to butyl methacrylate and methyl methacrylate groups is about 2:1:1.

Content of (dimethylamino)ethyl groups 20.8 per cent to 25.5 per cent (dried substance).

CHARACTERS

Appearance

Colourless or yellowish granules or white or almost white powder, slightly hygroscopic.

Solubility

Practically insoluble in water, freely soluble in methylene chloride. It dissolves slowly in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *basic butylated methacrylate copolymer CRS*.

B. It complies with the limits of the assay.

TESTS

Solution S

Dissolve 12.5 g in a mixture of 35.0 g of *acetone R* and 52.5 g of *2-propanol R*.

Viscosity (*2.2.10*)

www.webofpharma.com

https://thuocngocanh.com/

3 mPa·s to 6 mPa·s, determined on solution S.

Apparatus Rotating viscometer.

Dimensions:

— *spindle*: diameter = 25.15 mm, height = 90.74 mm, shaft diameter = 4 mm;

— *cylinder*: diameter = 27.62 mm, height = 0.135 m.

Rotating speed 30 r/min.

Volume of solution 16 mL of solution S.

Temperature 20 °C.

Absorbance (2.2.25)

Maximum 0.30 at 420 nm, determined on solution S.

Appearance of a film

Spread 1.0 mL of solution S evenly on a glass plate. Upon drying a clear film is formed.

Monomers

Maximum 0.1 per cent for each monomer (butyl methacrylate, methyl methacrylate and 2-(dimethylamino)ethyl methacrylate), determined by procedures A and B.

A. Butyl methacrylate and methyl methacrylate. Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, phosphate buffer solution pH 2.0 R (40:60 *V/V*).

Test solution Dissolve 1.00 g of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution Dissolve 20.0 mg of butyl methacrylate CRS (impurity A) and 10.0 mg of methyl methacrylate CRS (impurity B) in 3.0 mL of butanol R and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 250.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (7 µm).

Mobile phase phosphate buffer solution pH 2.0 R, methanol R2 (45:55 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 205 nm.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Injection 50 µL.

System suitability Reference solution:

— *resolution*: minimum 5 between the peaks due to impurities A and B.

Calculate the percentage contents of impurities A and B using the following expression:

$$100 \times 10^{-6} \times 50 \times \frac{C}{M} \times \frac{A_T}{A_R}$$

C	=	concentration of the monomer in the reference solution, in micrograms per millilitre;
M	=	mass of substance to be examined in the test solution, in grams;
A_T	=	area of the peak due to the monomer in the chromatogram obtained with the test solution;
A_R	=	area of the peak due to the monomer in the chromatogram obtained with the reference solution.

B. 2-(Dimethylamino)ethyl methacrylate. Liquid chromatography (*2.2.29*).

Test solution Dissolve 1.00 g of the substance to be examined in *tetrahydrofuran R* and dilute to 50.0 mL with the same solvent.

Reference solution Dissolve 10.0 mg of *2-(dimethylamino)ethyl methacrylate CRS* (impurity C) in *tetrahydrofuran R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 50.0 mL with *tetrahydrofuran R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 25 volumes of a 3.404 g/L solution of *potassium dihydrogen phosphate R* and 75 volumes of *tetrahydrofuran R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 50 µL.

Calculate the percentage content of impurity C as described under procedure A.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 110 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

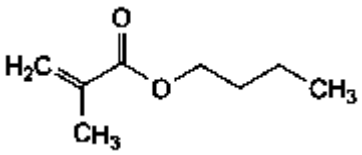
Dissolve 0.200 g in a mixture of 4 mL of *water R* and 96 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 7.21 mg of $C_4H_{10}N$.

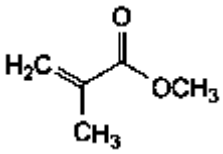
STORAGE

In an airtight container.

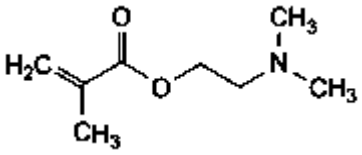
IMPURITIES



A. butyl 2-methylprop-2-enoate (butyl methacrylate),



B. methyl 2-methylprop-2-enoate (methyl methacrylate),



C. 2-(dimethylamino)ethyl 2-methylprop-2-enoate (2-(dimethylamino)ethyl methacrylate).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for basic butylated methacrylate copolymer used as film former in tablets.

Viscosity

https://thuvienthuocngocanh.com/

(see Tests).

Appearance of a film

(see Tests).

Solubility of a film

Take the film obtained in the test for appearance of a film (see Tests), place it in a flask containing a 10.3 g/L solution of *hydrochloric acid R* and stir. It dissolves within 1 h. Take another film, place it in a flask containing phosphate buffer solution pH 6.8 R and stir. It does not dissolve within 2 h.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Beclometasone Aqueous Nasal Spray

General Notices

Beclometasone Nasal Spray

Action and use

Glucocorticoid.

DEFINITION

Beclometasone Aqueous Nasal Spray is an aqueous suspension of either Beclometasone Dipropionate or Beclometasone Dipropionate Monohydrate in a suitable container fitted with an appropriate nasal delivery system.

The liquid nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of beclometasone dipropionate, $C_{28}H_{37}ClO_7$

80.0 to 120.0% of the amount stated to be delivered by actuation of the valve.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Evaporate a quantity of the nasal spray containing the equivalent of 0.5 mg of beclometasone dipropionate to dryness and dissolve the residue in 0.5 mL of *acetone*.

(2) 0.1% w/v of *beclometasone dipropionate BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to the peak due to beclometasone dipropionate in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *acetone*.

www.webofpharma.com

https://thuocngocanh.com/

(1) Evaporate a quantity of the nasal spray containing the equivalent of 0.5 mg of beclometasone dipropionate to dryness and dissolve the residue in 2 mL of *acetone*. Evaporate the solution to a volume such that the whole solution can be applied to the plate.

(2) 0.1% w/v of *beclometasone dipropionate BPCRS*.

(3) Dilute 1 volume of solution (2) to 2 volumes.

(4) Dilute 1 volume of solution (2) to 4 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase described below.

(c) Apply separately to the plate the whole of solution (1) and 10 µL of each of solutions (2), (3) and (4).

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *alkaline tetrazolium blue solution* and heat at 50° for 5 minutes. Cool and spray again with *alkaline tetrazolium blue solution*.

MOBILE PHASE

3 volumes of *methanol* and 97 volumes of *1,2-dichloroethane*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (2%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (1%);

not more than two such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.5%).

Disregard any spot with an Rf value of more than 0.85.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Discharge the container a sufficient number of times to obtain the equivalent of 0.5 mg of beclometasone dipropionate, add 30 mL of mobile phase, mix with the aid of ultrasound, dilute to 50 mL with mobile phase and filter. Dilute 3 volumes of this solution to 20 volumes with the mobile phase.

(2) 0.00015% w/v of *beclometasone dipropionate BPCRS* in the mobile phase.

(3) 0.00015% w/v each of *testosterone propionate BPCRS* and *beclometasone dipropionate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 50°.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *water* and 70 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the average content of $C_{28}H_{37}ClO_7$ delivered by a single actuation of the valve using the declared content of $C_{28}H_{37}ClO_7$ in *beclometasone dipropionate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of beclometasone dipropionate.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Beclometasone Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Beclometasone Cream contains Beclometasone Dipropionate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of beclometasone dipropionate, $C_{28}H_{37}ClO_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the preparation being examined containing 0.5 mg of Beclometasone Dipropionate in 20 mL of *methanol (80%)* by heating on a water bath until the methanol begins to boil. Shake vigorously, cool in ice for 30 minutes and centrifuge. Mix 10 mL of the supernatant liquid with 3 mL of *water* and 5 mL of *chloroform*, shake vigorously, allow the layers to separate, evaporate the chloroform layer to dryness in a current of nitrogen with gentle heating and dissolve the residue in 1 mL of *chloroform*.

(2) 0.025% w/v of *beclometasone dipropionate BPCRS* in *chloroform*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air until the solvent has evaporated, heat at 105° for 5 minutes and, while hot, spray with *alkaline tetrazolium blue solution*.

MOBILE PHASE

100 volumes of *chloroform*, 10 volumes of *acetone* and 5 volumes of *absolute ethanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to beclometasone dipropionate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For creams containing 0.025% w/w of Beclometasone Dipropionate.

(1) Mix 10 mL of *methanol (80%)* containing 0.01% w/v of *beclometasone dipropionate BPCRS* and 0.0005% w/v of *beclometasone 17-propionate BPCRS* with 2 mL of a 0.05% w/v solution of *testosterone propionate* (internal standard) in *methanol (80%)* and dilute to 50 mL with the same solvent.

(2) Disperse a quantity of the preparation being examined containing 1 mg of Beclometasone Dipropionate in 20 mL of hot *methanol (90%)*, add 25 mL of *2,2,4-trimethylpentane*, cool, shake the mixture and filter the lower layer through a small plug of absorbent cotton previously washed with *methanol (80%)*. Repeat the extraction of the trimethylpentane solution with two further 10 mL quantities of *methanol (80%)*, filtering the extracts through the absorbent cotton. Combine the extracts and add sufficient *methanol (80%)* to produce 50 mL. If the resulting solution is more than slightly cloudy, filter.

(3) Prepare in the same manner as solution (2) but add 2 mL of a 0.05% w/v solution of the internal standard in *methanol (80%)* before diluting to 50 mL.

For creams containing 0.5% w/w of Beclometasone Dipropionate.

(1) Mix 25 mL of *methanol (80%)* containing 0.04% w/v of *beclometasone dipropionate BPCRS* and 0.002% w/v of *beclometasone 17-propionate BPCRS* with 20 mL of a 0.05% w/v solution of *testosterone propionate* (internal standard) in *methanol (80%)* and dilute to 200 mL with the same solvent.

(2) Add 100 mL of *methanol (80%)* to a quantity of the preparation being examined containing 10 mg of Beclometasone Dipropionate and heat on a water bath, with swirling, until the preparation has dispersed. Cool, dilute to 200 mL with *methanol (80%)* and filter.

(3) Prepare in the same manner as solution (2) but add 20 mL of a 0.05% w/v solution of the internal standard in *methanol (80%)* before diluting to 200 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of *methanol* and *water* such that the *resolution factor* between the peaks due to beclometasone 17-propionate (retention time about 1.5 minutes) and beclometasone dipropionate (retention time about 2 minutes) is greater than 2.0 (a mixture of 70 volumes of *methanol* and 30 volumes of *water* is usually suitable).

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (1), the *resolution factor* between the peaks due to beclometasone 17-propionate (retention time about 1.5 minutes) and beclometasone dipropionate (retention time about 2 minutes) is greater than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{37}ClO_7$ in the preparation being examined using the declared content of $C_{28}H_{37}ClO_7$ in *beclometasone dipropionate BPCRS*.

STORAGE

Beclometasone Cream should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

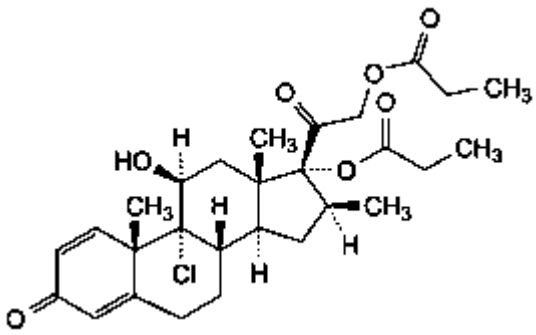
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Beclometasone Dipropionate

General Notices

Anhydrous Beclometasone Dipropionate

(Ph. Eur. monograph 0654)



$C_{28}H_{37}ClO_7$ 521.0 *5534-09-8*

Action and use

Glucocorticoid.

Preparations

Beclometasone Cream

Beclometasone Aqueous Nasal Spray

Beclometasone Inhalation Powder

Beclometasone Inhalation Powder, pre-metered

Beclometasone Ointment

Beclometasone Pressurised Inhalation

Ph Eur

DEFINITION

9-Chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate.

Content

www.webofpharma.com

https://thuocngocanh.com/

96.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *anhydrous beclometasone dipropionate CRS*.

B. Treat 25 mg by the oxygen-flask method (*2.5.10*). Use a mixture of 1 mL of *1 M sodium hydroxide* and 20 mL of *water R* to absorb the combustion products. The solution gives reaction (a) of chlorides (*2.3.1*).

C. Loss on drying (see Tests).

TESTS

Specific optical rotation (*2.2.7*)

+ 108 to + 115 (dried substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase A, mobile phase B (45:55 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in 28 mL of mobile phase B and dilute to 50.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 5.0 mL of test solution (b) to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *beclometasone dipropionate for system suitability CRS* (containing impurity D) in 3 mL of mobile phase B and dilute to 5 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of *beclometasone dipropionate for peak identification CRS* (containing impurities A, B, C, L and M) in 3 mL of mobile phase B and dilute to 5 mL with mobile phase A. Use 1 mL of this solution to dissolve the contents of a vial of *beclometasone dipropionate impurities F and N CRS*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dissolve 50.0 mg of *anhydrous beclometasone dipropionate CRS* in 28 mL of mobile phase B and dilute to 50.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, *Ø* = 4.6 mm;

— *stationary phase*: spherical difunctional bonded *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: 2.72 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 2.35 with *phosphoric acid R*;

— *mobile phase B*: *tetrahydrofuran R*, *acetonitrile R*, *methanol R* (5:23:25 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	40	60
4 - 12	40 → 45	60 → 55
12 - 59	45	55

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µl of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *beclometasone dipropionate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, F, L, M and N; use the chromatogram supplied with *beclometasone dipropionate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to beclometasone dipropionate (retention time = about 25 min): impurity A = about 0.3; impurity B = about 0.6; impurity D = about 1.1; impurity M = about 1.2; impurity L = about 1.3; impurity C = about 1.8; impurity N = about 2.0; impurity F = about 2.2.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to beclometasone dipropionate.

Limits:

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity F = 1.3; impurity M = 2.0;

— *impurity L*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *impurities B, F, M*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities A, D, N*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{28}H_{37}ClO_7$ from the declared content of *anhydrous beclometasone dipropionate CRS*.

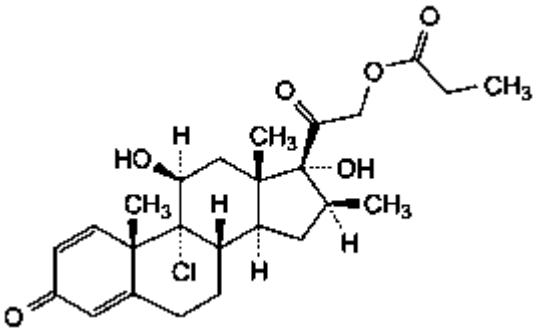
IMPURITIES

Specified impurities *A, B, C, D, F, L, M, N.*

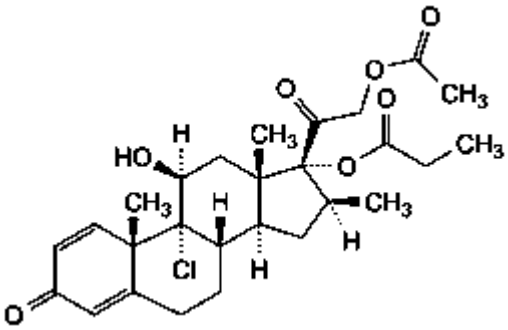
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, H, I, J, O, Q, R, S, U, V.*

www.webofpharma.com

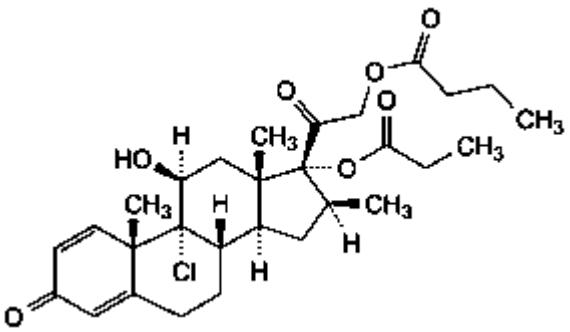
https://thuocngocanh.com/



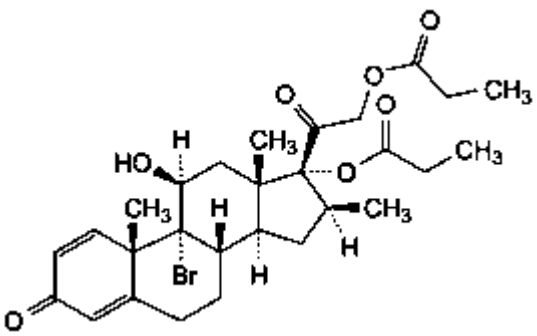
A. 9-chloro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl propanoate (beclometasone 21-propionate),



B. 21-(acetyloxy)-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (beclometasone 21-acetate 17-propionate),



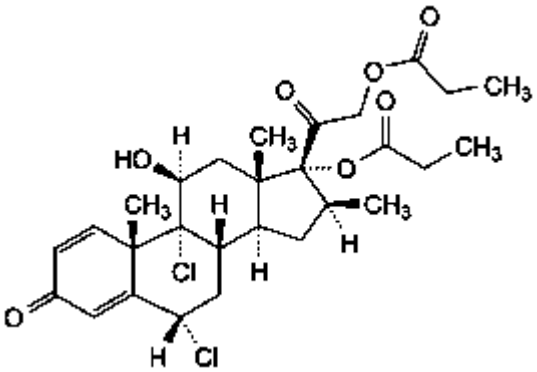
C. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxo-17-(propanoyloxy)-pregna-1,4-dien-21-yl butanoate (beclometasone 21-butyrate 17-propionate),



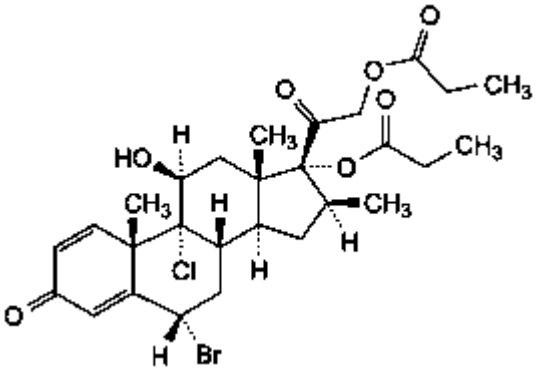
D. 9-bromo-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

www.webofpharma.com

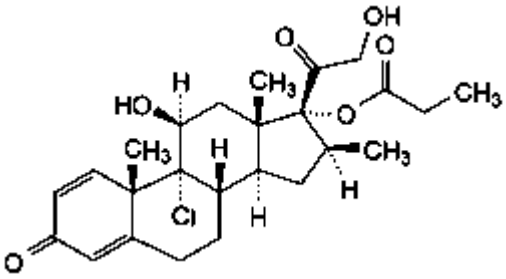
https://thuocngocanh.com/



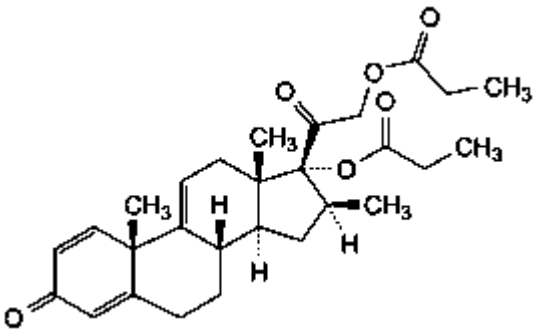
E. 6α,9-dichloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



F. 6α-bromo-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



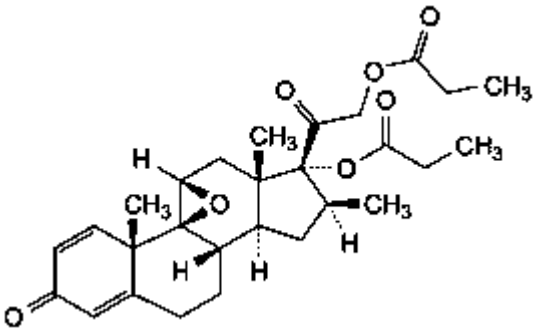
H. 9-chloro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (beclometasone 17-propionate),



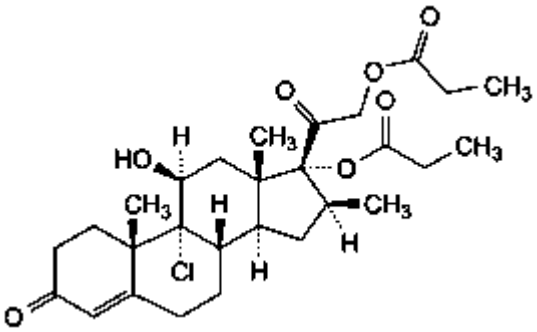
I. 16β-methyl-3,20-dioxopregna-1,4,9(11)-triene-17,21-diyl dipropanoate,

www.webofpharma.com

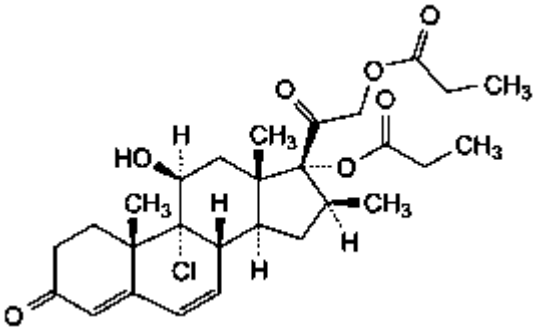
https://thuocngocanh.com/



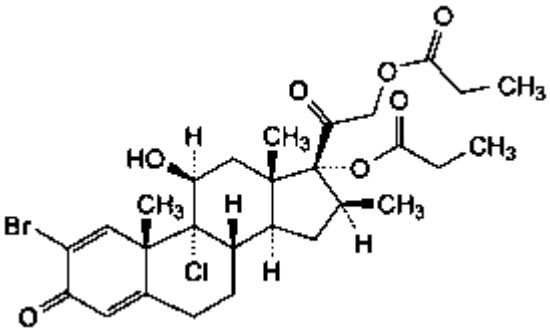
J. 9,11β-epoxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-diene-17,21-diyl dipropanoate,



L. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregn-4-ene-17,21-diyl dipropanoate,



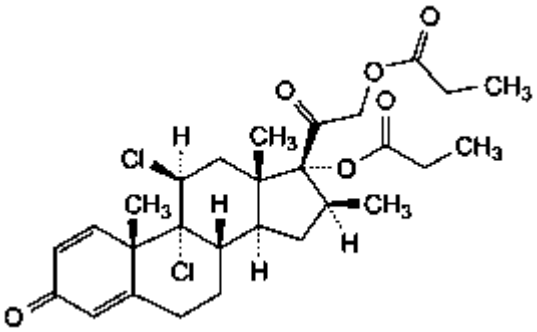
M. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-4,6-diene-17,21-diyl dipropanoate,



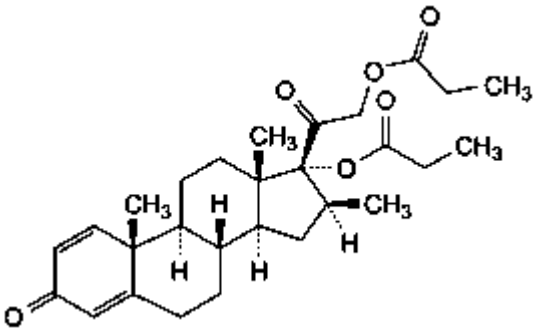
N. 2-bromo-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

www.webofpharma.com

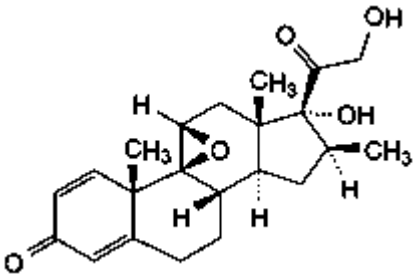
https://thuocngocanh.com/



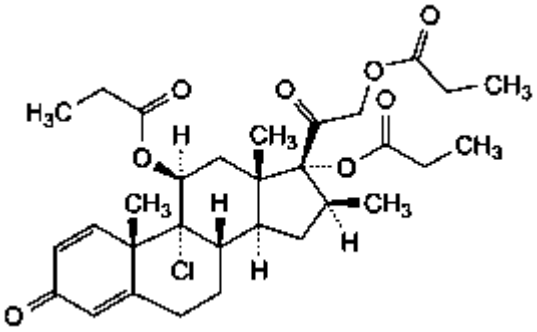
O. 9,11β-dichloro-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



Q. 16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



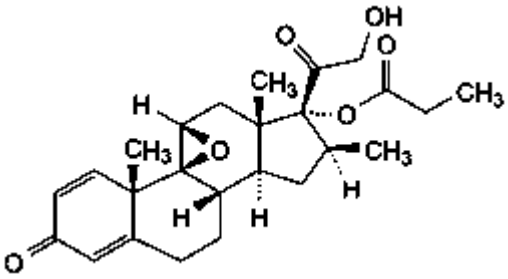
R. 9,11β-epoxy-17,21-dihydroxy-16β-methyl-9β-pregna-1,4-diene-3,20-dione,



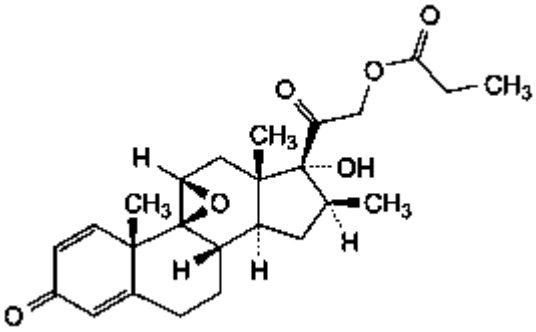
S. 9-chloro-16β-methyl-3,20-dioxopregna-1,4-diene-11β,17,21-triyl tripropanoate (beclometasone tripropionate),

www.webofpharma.com

https://thuocngocanh.com/



U. 9,11β-epoxy-21-hydroxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-dien-17-yl propanoate,



V. 9,11β-epoxy-17-hydroxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-dien-21-yl propanoate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

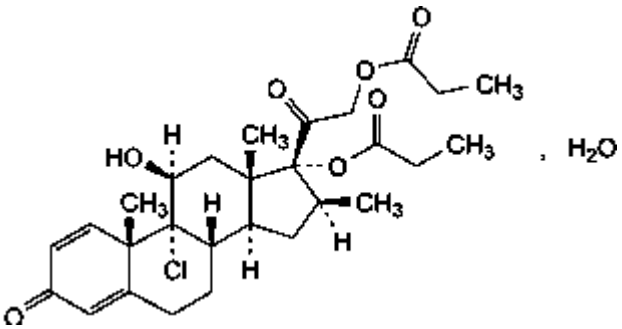
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Beclometasone Dipropionate Monohydrate

General Notices

(Ph. Eur. monograph 1709)



$C_{28}H_{37}ClO_7,H_2O$ 539.1

Action and use

Glucocorticoid.

Preparations

Beclometasone Aqueous Nasal Spray

Beclometasone Inhalation Powder

Beclometasone Inhalation Powder, pre-metered

Ph Eur

DEFINITION

9-Chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate monohydrate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *beclometasone dipropionate monohydrate CRS*.

B. Treat 25 mg by the oxygen-flask method (2.5.10). Use a mixture of 1 mL of *1 M sodium hydroxide* and 20 mL of *water R* to absorb the combustion products. The solution gives reaction (a) of chlorides (2.3.1).

C. Loss on drying (see Tests).

TESTS

Specific optical rotation (2.2.7)

+ 108 to + 115 (dried substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase A, mobile phase B (45:55 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in 28 mL of mobile phase B and dilute to 50.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 5.0 mL of test solution (b) to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *beclometasone dipropionate for system suitability CRS* (containing impurity D) in 3 mL of mobile phase B and dilute to 5 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of *beclometasone dipropionate for peak identification CRS* (containing impurities B, C and L) in 3 mL of mobile phase B and dilute to 5 mL with mobile phase A. Use 1 mL of this solution to dissolve the contents of a vial of *beclometasone dipropionate impurities F and N CRS*.

Reference solution (d) Dissolve 50.0 mg of *anhydrous beclometasone dipropionate CRS* in 28 mL of mobile phase B and dilute to 50.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical difunctional bonded *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: 2.72 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 2.35 with *phosphoric acid R*;

— *mobile phase B*: *tetrahydrofuran R*, *acetonitrile R*, *methanol R* (5:23:25 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	40	60
4 - 12	40 → 45	60 → 55
12 - 59	45	55

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µl of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *beclometasone dipropionate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, C, F and L; use the chromatogram supplied with *beclometasone dipropionate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to beclometasone dipropionate (retention time = about 25 min): impurity B = about 0.6; impurity D = about 1.1; impurity L = about 1.3; impurity C = about 1.8; impurity F = about 2.2.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to beclometasone dipropionate.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity F by 1.3;

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities C, F, L*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

2.8 per cent to 3.8 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

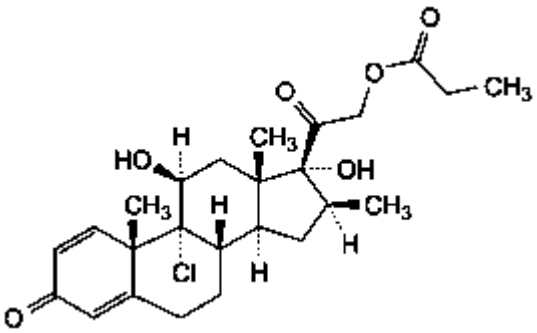
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{28}H_{37}ClO_7$ from the declared content of *anhydrous beclometasone dipropionate CRS*.

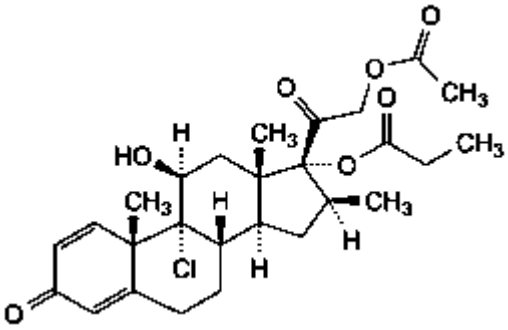
IMPURITIES

Specified impurities *B, C, F, L.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E, H, I, J, M, N, O, Q, R, S, U, V.*



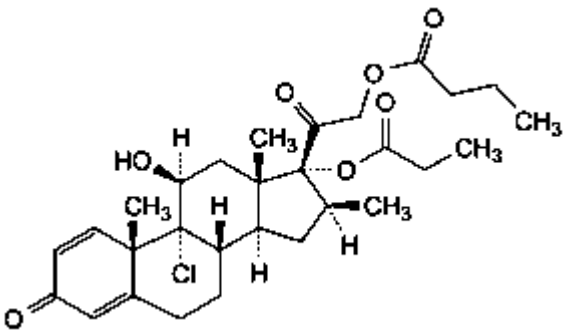
A. 9-chloro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl propanoate (beclometasone 21-propionate),



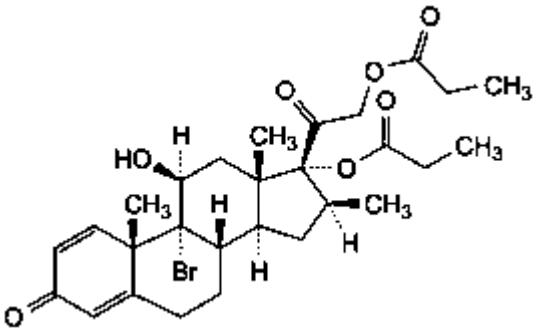
B. 21-(acetyloxy)-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (beclometasone 21-acetate 17-propionate),

www.webofpharma.com

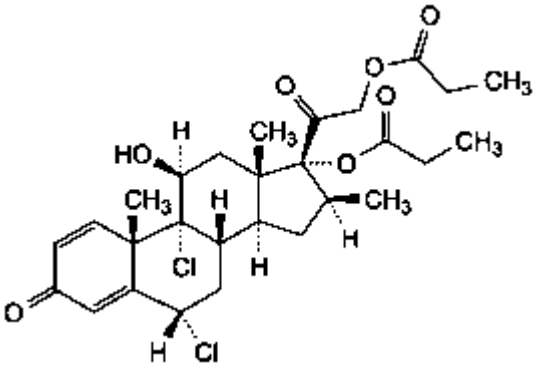
https://thuocngocanh.com/



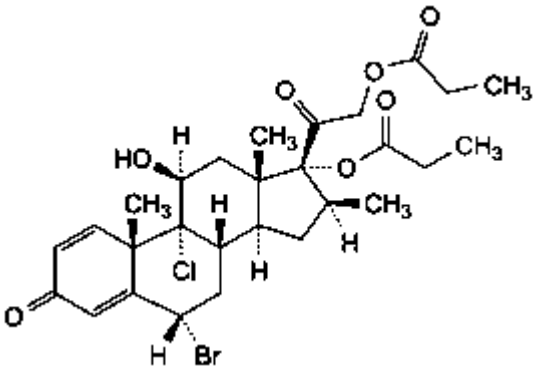
C. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxo-17-(propanoyloxy)-pregna-1,4-dien-21-yl butanoate (beclometasone 21-butyrate 17-propionate),



D. 9-bromo-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



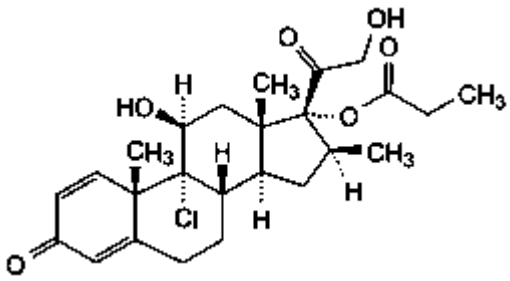
E. 6α,9-dichloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



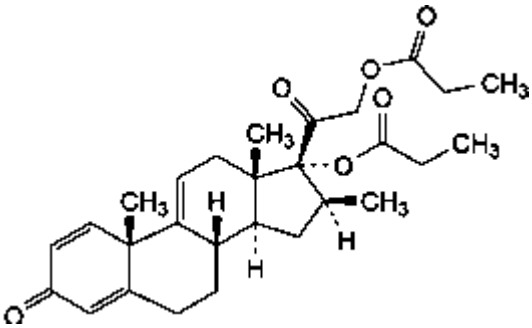
F. 6α-bromo-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

www.webofpharma.com

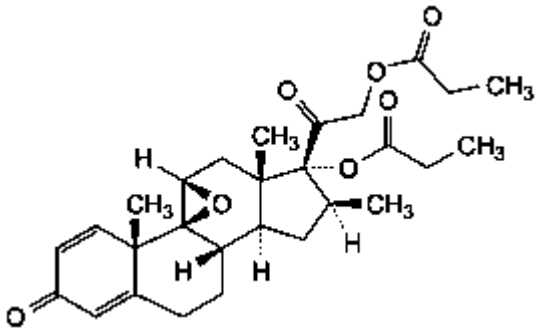
https://thuocngocanh.com/



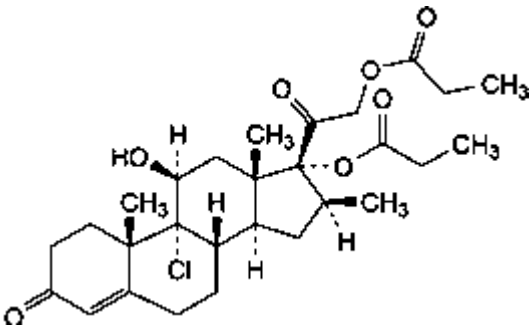
H. 9-chloro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (beclometasone 17-propionate),



I. 16β-methyl-3,20-dioxopregna-1,4,9(11)-triene-17,21-diyl dipropanoate,



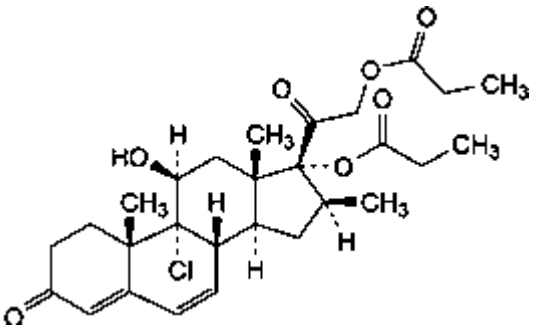
J. 9,11β-epoxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-diene-17,21-diyl dipropanoate,



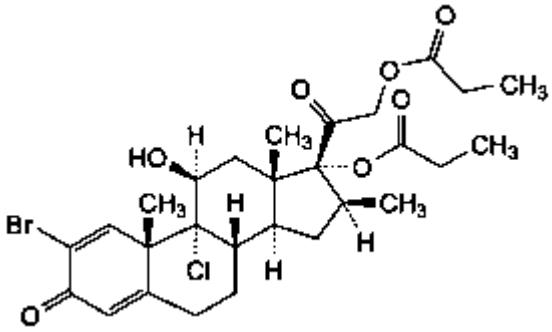
L. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregn-4-ene-17,21-diyl dipropanoate,

www.webofpharma.com

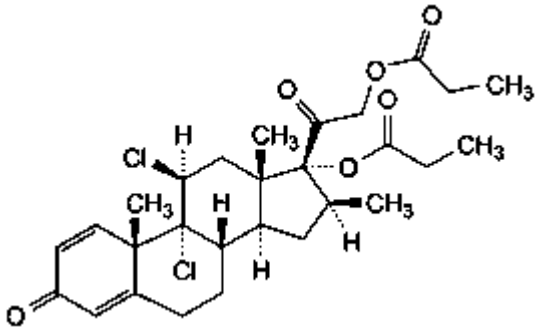
https://thuocngocanh.com/



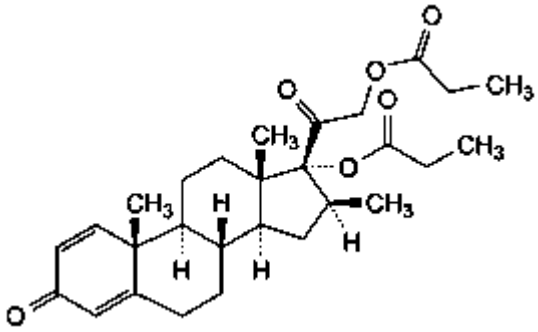
M. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-4,6-diene-17,21-diyl dipropanoate,



N. 2-bromo-9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



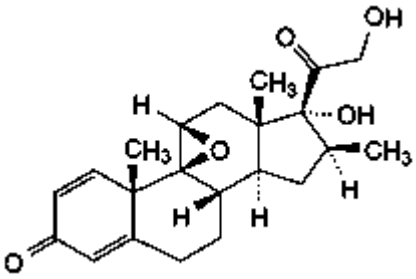
O. 9,11β-dichloro-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,



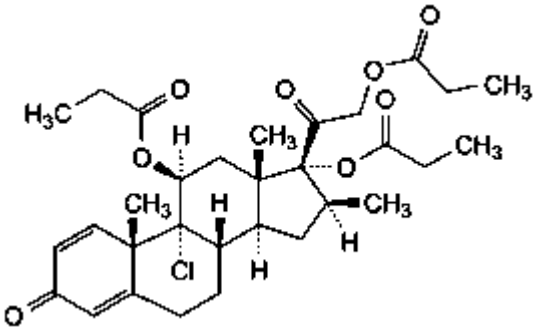
Q. 16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate,

www.webofpharma.com

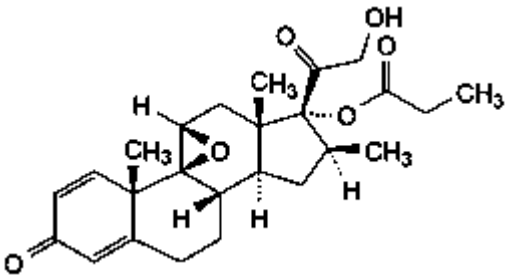
https://thuocngocanh.com/



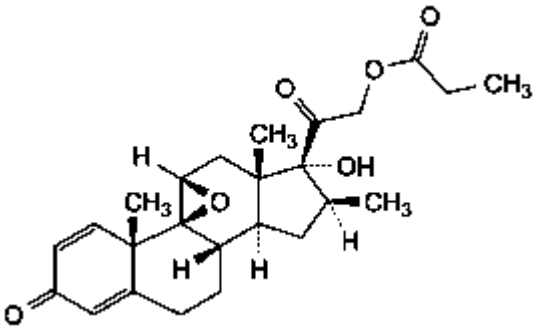
R. 9,11β-epoxy-17,21-dihydroxy-16β-methyl-9β-pregna-1,4-diene-3,20-dione,



S. 9-chloro-16β-methyl-3,20-dioxopregna-1,4-diene-11β,17,21-triyl tripropanoate (beclometasone tripropionate),



U. 9,11β-epoxy-21-hydroxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-dien-17-yl propanoate,



V. 9,11β-epoxy-17-hydroxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-dien-21-yl propanoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Beclometasone Inhalation Powder

General Notices

Beclometasone Powder for Inhalation, Metered-dose Powder Inhaler

Action and use

Glucocorticoid.

DEFINITION

Beclometasone Inhalation Powder consists of Beclometasone Dipropionate or Beclometasone Dipropionate Monohydrate in *microfine powder* or aerodynamically equivalent, either alone or combined with a suitable carrier. It is administered by a dry-powder inhaler.

The inhalation powder complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of beclometasone dipropionate, $C_{28}H_{37}ClO_7$

80.0 to 120.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. *For products containing lactose*; disperse 0.25 g of the inhalation powder in 5 mL of *water*. Add 5 mL of 6M *ammonia* and heat in a water-bath at 80° for 10 minutes. An orange-red colour is produced.

TESTS

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient of a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile* to produce a solution containing the equivalent of 0.00005% w/v of beclometasone dipropionate.

(2) Dilute 10 mL of a solution containing 0.0005% w/v of *beclometasone dipropionate BPCRS* in *methanol* to 100 mL with a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octylsilyl silica gel for chromatography* (5 µm) (Lichrospher 60 RP-select B is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

25 volumes of *water* and 75 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the amount of beclometasone dipropionate, $C_{28}H_{37}ClO_7$, per delivered dose using the declared content of $C_{28}H_{37}ClO_7$ in *beclometasone dipropionate BPCRS*. Repeat the procedure as described for reservoir systems under Inhalation Powders, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the inhalation powder containing the equivalent of 1.2 mg of beclometasone dipropionate in the mobile phase and dilute to 5 mL with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.0040% w/v each of *beclometasone 17-propionate BPCRS* and *beclometasone 21-propionate BPCRS* in the mobile phase.

(4) Dilute 1 volume of solution (2) to 20 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 or Lichrospher RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 100 µL of each solution.

(g) For solutions (1) and (2) allow the chromatography to proceed for twice the retention time of the principal peak.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

Dilute 60 volumes of *acetonitrile* to 100 volumes with *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time for beclometasone 17-propionate is about 6 minutes, for beclometasone 21-propionate, about 7 minutes and for beclometasone dipropionate, about 13 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to beclometasone 17-propionate and beclometasone 21-propionate is at least 1.4. If necessary adjust the concentration of *acetonitrile* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

not more than one such peak has an area greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of beclometasone dipropionate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Beclometasone Inhalation Powder, pre-metered

General Notices

Beclometasone Powder for Inhalation, pre-dispensed

Action and use

Glucocorticoid.

DEFINITION

Beclometasone Inhalation Powder, pre-metered consists of Beclometasone Dipropionate or Beclometasone Dipropionate Monohydrate in *microfine powder* either alone or combined with a suitable carrier. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, pre-metered complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of beclometasone dipropionate, $C_{28}H_{37}ClO_7$

When supplied as disks, 90.0 to 110.0% of the stated amount per pre-metered unit. When supplied as capsules, 80.0 to 120.0% of the stated amount per pre-metered unit.

IDENTIFICATION

A. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. Disperse a quantity of powder, containing the equivalent of 200 µg of beclometasone dipropionate in 5 mL of 1M *sodium hydroxide* in a 25 mL conical flask. Add three drops of *copper sulfate solution* and shake. A precipitate may form which dissolves to give a clear blue solution. Heat the solution to boiling; a red precipitate is produced.

C. *For products containing lactose* disperse 0.25 g of the powder for inhalation in 5 mL of *water*. Add 5 mL of 6M *ammonia* and heat in a water-bath at 80° for 10 minutes. An orange-red colour is produced.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient of a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile* to produce a solution containing the equivalent of 0.00005% w/v of beclometasone dipropionate.
(2) Dilute 10 mL of a solution containing 0.0005% w/v of *beclometasone dipropionate BPCRS* in *methanol* to 100 mL with a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octylsilyl silica gel for chromatography* (5 µm) (Lichrospher 60 RP-select B is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 100 µL of each solution.

MOBILE PHASE

25 volumes of *water* and 75 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of beclometasone dipropionate, $C_{28}H_{37}ClO_7$, per delivered dose using the declared content of $C_{28}H_{37}ClO_7$ in *beclometasone dipropionate BPCRS*. Repeat the procedure as described for pre-metered systems under Inhalation Powders, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of 20 units containing the equivalent of 1.2 mg of beclometasone dipropionate in the mobile phase and dilute to 5 mL with the mobile phase.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(3) 0.0040% w/v each of *beclometasone 17-propionate BPCRS* and *beclometasone 21-propionate BPCRS* in the mobile phase.
(4) Dilute 1 volume of solution (2) to 20 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 or Lichrospher RP18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 100 µL of each solution.

(g) For solutions (1) and (2) allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

Dilute 60 volumes of *acetonitrile* to 100 volumes with *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time for beclometasone 17-propionate is about 6 minutes, for beclometasone 21-propionate, about 7 minutes and for beclometasone dipropionate, about 13 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to beclometasone 17-propionate and beclometasone 21-propionate is at least 1.4. If necessary adjust the concentration of *acetonitrile* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

not more than one such *secondary peak* has an area greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder the contents of 20 pre-dispensed units. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of the pre-dispensed unit in sufficient of the mobile phase to produce a solution containing the equivalent of 0.001% w/v of beclometasone dipropionate.

(2) 0.001% w/v of *beclometasone dipropionate BPCRS* in the mobile phase.

(3) 0.001% w/v each of *beclometasone 17-propionate BPCRS* and *beclometasone 21-propionate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to beclometasone 17-propionate and beclometasone 21-propionate is at least 1.4. If necessary adjust the concentration of *acetonitrile* in the mobile phase.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{28}H_{37}ClO_7$ using the declared content of $C_{28}H_{37}ClO_7$ in *beclometasone dipropionate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of beclometasone dipropionate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Beclometasone Ointment

General Notices

Action and use

Glucocorticoid.

DEFINITION

Beclometasone Ointment contains Beclometasone Dipropionate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of beclometasone dipropionate, $C_{28}H_{37}ClO_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the ointment containing 0.5 mg of Beclometasone Dipropionate in 2 mL of *chloroform* by heating on a water bath, add 10 mL of *methanol* and heat on the water bath until the mixture begins to boil. Shake vigorously, cool in ice for 30 minutes and filter. Evaporate the filtrate to dryness in a current of nitrogen with gentle heating and dissolve the residue in 1 mL of *chloroform*.

(2) 0.05% w/v of *beclometasone dipropionate BPCRS* in *chloroform*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air until the solvent has evaporated, heat at 105° for 5 minutes and, while hot, spray with *alkaline tetrazolium blue solution*.

MOBILE PHASE

5 volumes of *absolute ethanol*, 10 volumes of *acetone* and 100 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to beclometasone dipropionate in the chromatogram obtained with solution (1).

ASSAY

(1) Disperse a quantity of the ointment containing 1 mg of Beclometasone Dipropionate in 25 mL of hot *2,2,4-trimethylpentane*, cool and extract the mixture with successive quantities of 20, 10 and 10 mL of *methanol (80%)*, filtering each extract in turn through a small plug of absorbent cotton previously washed with *methanol (80%)*. Combine the filtrates and dilute to 50 mL with *methanol (80%)*.

(2) Mix 10 mL of *methanol (80%)* containing 0.01% w/v of *beclometasone dipropionate BPCRS* and 0.0005% w/v of *beclometasone 17-propionate BPCRS* with 2 mL of a 0.05% w/v solution of *testosterone propionate* (internal standard) in *methanol (80%)* and dilute to 50 mL with the same solvent.

(3) Prepare solution (3) in the same manner as solution (1) but add 2 mL of a 0.05% w/v solution of the internal standard in *methanol (80%)* before diluting to 50 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of *methanol* and *water* such that the *resolution factor* between the peaks due to beclometasone 17-propionate (retention time about 1.5 minutes) and beclometasone dipropionate (retention time about 2 minutes) is greater than 2.0 (a mixture of 30 volumes of *water* and 70 volumes of *methanol* is usually suitable).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to beclometasone 17-propionate (retention time about 1.5 minutes) and beclometasone dipropionate (retention time about 2 minutes) is greater than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{37}ClO_7$ in the preparation being examined using the declared content of $C_{28}H_{37}ClO_7$ in *beclometasone dipropionate BPCRS*.

STORAGE

Beclometasone Ointment should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Beclometasone Pressurised Inhalation

General Notices

Beclometasone Pressurised Inhalations from different manufacturers, whilst complying with the requirements of the monograph, are not necessarily interchangeable.

Action and use

Glucocorticoid.

DEFINITION

Beclometasone Pressurised Inhalation is a solution or suspension of Beclometasone Dipropionate in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7 Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of beclometasone dipropionate, $C_{28}H_{37}ClO_7$

85.0 to 115.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of beclometasone dipropionate (2) (*RS 379*). Examine the substance as a dispersion in *potassium bromide* prepared in the following manner. Discharge the container a sufficient number of times, under conditions of very low relative humidity (less than 5%), into a mortar to obtain 2 mg of Beclometasone Dipropionate. Heat at 110° for 2 hours at a pressure of 2 kPa, cool, grind the residue thoroughly with 0.1 g of *potassium bromide*, add a further 0.2 g of *potassium bromide* and mix thoroughly.

TESTS

Uniformity of delivered dose

www.webofpharma.com

https://thuocngocanh.com/

Complies with the requirements stated under Pressurised Metered-dose Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.272% w/v of *potassium dihydrogen orthophosphate*.

(1) Collect single doses of the preparation being examined using the procedure described under *Pressurised Metered-dose Preparations for Inhalation*, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol (70%)* to produce a solution containing 0.00025% w/v of Beclometasone Dipropionate.

(2) 0.00025% w/v of *Beclometasone Dipropionate BPCRS* in *methanol (70%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (50 mm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Sunfire C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 239 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

52 volumes of *tetrahydrofuran*, 240 volumes of *acetonitrile*, 260 volumes of *methanol* and 450 volumes of Solution A. Adjust the final pH to 3.25 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of the peak due to beclometasone is about 8 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the column efficiency of the peak due to beclometasone dipropionate is at least 2000 theoretical plates.

DETERMINATION OF CONTENT

Calculate the content of beclometasone dipropionate, $C_{28}H_{37}ClO_7$, per delivered dose from the chromatograms obtained and using the declared content of $C_{28}H_{37}ClO_7$, in *beclometasone dipropionate BPCRS*. Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *acetone*.

(1) Discharge the container into a small, dry flask a sufficient number of times to obtain 0.5 mg of Beclometasone Dipropionate and dissolve the residue in 2 mL of *acetone*. Evaporate the solution to a volume such that the whole solution can be applied to the plate.

(2) 0.1% w/v of *beclometasone dipropionate BPCRS*.

(3) Dilute 1 volume of solution (2) to 2 volumes.

(4) Dilute 1 volume of solution (2) to 4 volumes.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase described below.

(c) Apply separately to the plate the whole of solution (1) and 10 µL of each of solutions (2), (3) and (4).

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *alkaline tetrazolium blue solution* and heat at 50° for 5 minutes. Cool and spray again with *alkaline tetrazolium blue solution*.

MOBILE PHASE

3 volumes of *methanol* and 97 volumes of *1,2-dichloroethane*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (2%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (1%);

not more than two such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.5%).

Disregard any spot with an Rf value of more than 0.85.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of delivered dose.

LABELLING

The label states the content of active ingredient in terms of the equivalent delivered dose.

© Crown Copyright 2022

www.webofpharma.com

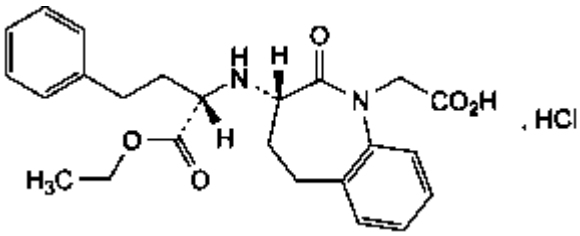
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benazepril Hydrochloride

General Notices

(Ph. Eur. monograph 2388)



$C_{24}H_{29}ClN_2O_5$ 461.0 *86541-74-4*

Action and use

Angiotensin converting enzyme inhibitor.

Ph Eur

DEFINITION

[(3*S*)-3-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid hydrochloride.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Slightly soluble in water, freely soluble in anhydrous ethanol, very slightly soluble in ethyl acetate, practically insoluble in cyclohexane.

It shows polymorphism (*5.9*).

IDENTIFICATION

Carry out either tests A, B, D or tests B, C, D.

https://nhathuocngocanh.com/

A. Specific optical rotation (2.2.7): -141 to -136 (dried substance).

Dissolve 1.000 g in anhydrous ethanol R and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison benazepril hydrochloride CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

C. Enantiomeric purity (see Tests).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of benazepril hydrochloride CRS in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of benazepril for system suitability CRS (containing impurities B, C, D, E, F and G) in 1.0 mL of test solution (a).

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.30 m, Ø = 3.9 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (10 µm).

Mobile phase Add 0.2 mL of glacial acetic acid R to 1000 mL of a mixture of 360 volumes of water R and 640 volumes of methanol R2; add 0.81 g of tetrabutylammonium bromide R and stir to dissolve.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 25 µL of test solution (a) and reference solutions (b) and (c).

Run time 3 times the retention time of benazepril.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to benazepril (retention time = about 6 min): impurity E = about 0.3; impurity F = about 0.4; impurity C = about 0.5; impurity B = about 1.8; impurity D = about 2.0; impurity G = about 2.5.

Identification of impurities Use the chromatogram supplied with *benazepril for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D, E, F and G.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to benazepril and impurity B and minimum 1.5 between the peaks due to impurities E and F.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.5; impurity F = 0.7;

— *impurity B*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities D, E, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Enantiomeric purity

Liquid chromatography (*2.2.29*).

Buffer solution pH 6.0 Dissolve 3.58 g of *disodium hydrogen phosphate dodecahydrate R* and 9.66 g of *potassium dihydrogen phosphate R* in *water R* and dilute to 1000.0 mL with the same solvent.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *benazepril impurity A CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: spherical *silica gel AGP for chiral chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *methanol R2*, buffer solution pH 6.0 (20:80 *V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 50 µL of the test solution and reference solutions (b) and (c).

Run time 3.5 times the retention time of benazepril.

Relative retention With reference to benazepril (retention time = about 6 min): impurity A = about 1.9.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to benazepril.

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Loss on drying (*2.2.32*)

Maximum 1.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{24}H_{29}ClN_2O_5$ from the declared content of *benazepril hydrochloride CRS*.

STORAGE

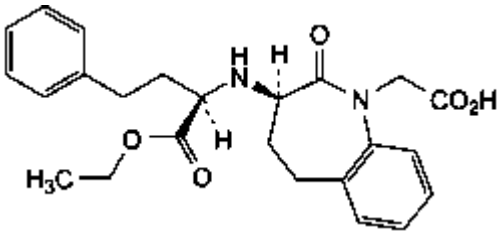
Protected from light, in an airtight container.

www.webofpharma.com

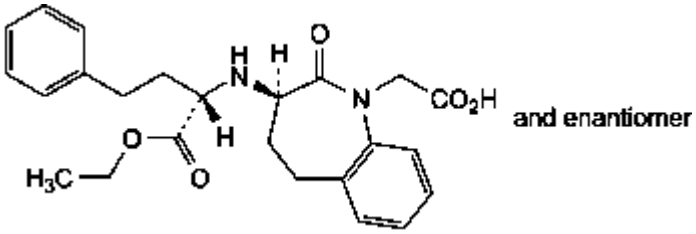
https://thuocngocanh.com/

IMPURITIES

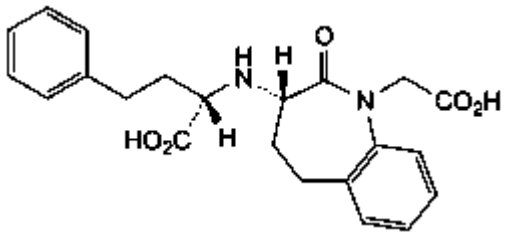
Specified impurities A, B, C, D, E, F, G.



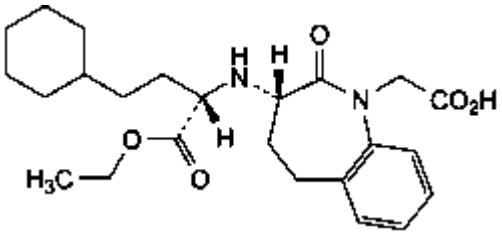
A. [(3*R*)-3-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid,



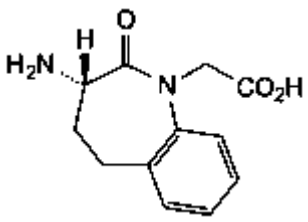
B. [(3*RS*)-3-[[(1*SR*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid,



C. (2*S*)-2-[[(3*S*)-1-(carboxymethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoic acid,



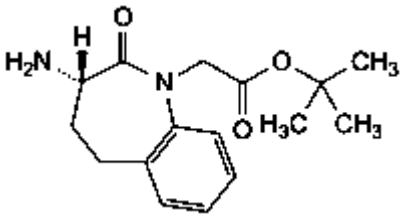
D. [(3*S*)-3-[[(1*S*)-3-cyclohexyl-1-(ethoxycarbonyl)propyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid,



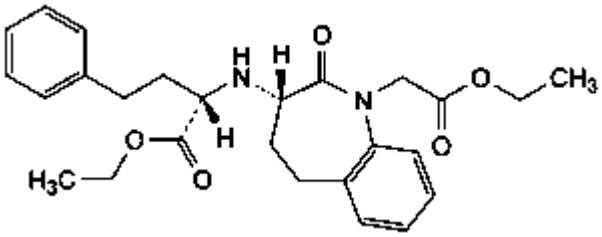
E. [(3*S*)-3-amino-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid,

www.webofpharma.com

https://thuocngocanh.com/



F. 1,1-dimethylethyl [(3*S*)-3-amino-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetate,



G. ethyl (2*S*)-2-[[(3*S*)-1-(2-ethoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

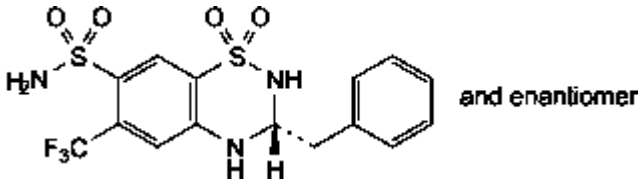
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bendroflumethiazide

General Notices

(Ph. Eur. monograph 0370)



$C_{15}H_{14}F_3N_3O_4S_2$ 421.4 *73-48-3*

Action and use

Thiazide diuretic.

Preparations

Bendroflumethiazide Tablets

Bendroflumethiazide Oral Suspension

Ph Eur

DEFINITION

(3*RS*)-3-Benzyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison bendroflumethiazide CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture Mix 40 volumes of methanol R and 60 volumes of a 2.0 g/L solution of citric acid monohydrate R.

Test solution Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of bendroflumethiazide impurity A CRS and 2.5 mg of altizide CRS in the solvent mixture and dilute to 10 mL with the solvent mixture. Mix 1 mL of this solution with 1 mL of the test solution and dilute to 100 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 15 volumes of tetrahydrofuran R, 25 volumes of methanol R and 60 volumes of a 2.0 g/L solution of citric acid monohydrate R.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 273 nm.

Injection 20 µL.

Run time Twice the retention time of bendroflumethiazide.

Relative retention With reference to bendroflumethiazide (retention time = about 8 min): impurity A = about 0.2; altizide = about 0.5.

System suitability Reference solution (a):

— resolution: minimum 10 between the peaks due to altizide and bendroflumethiazide.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

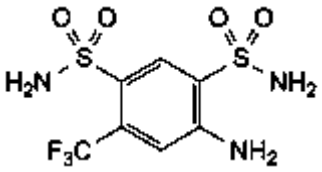
ASSAY

Dissolve 0.150 g in 50 mL of *dimethyl sulfoxide R*. Titrate to the 2nd point of inflexion with *0.1 M tetrabutylammonium hydroxide in 2-propanol*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 21.07 mg of $C_{15}H_{14}F_3N_3O_4S_2$.

IMPURITIES

Specified impurities A.



A. 4-amino-6-(trifluoromethyl)benzene-1,3-disulfonamide.

Ph Eur

© Crown Copyright 2022

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bendroflumethiazide Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Thiazide diuretic.

DEFINITION

Bendroflumethiazide Oral Suspension is a suspension of Bendroflumethiazide in a suitable flavoured aqueous vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of bendroflumethiazide, $C_{15}H_{14}F_3N_3O_4S_2$

92.5 to 105.0% of the stated amount.

Shake the oral suspension vigorously before carrying out the following tests.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix a quantity of the oral suspension with sufficient *acetone* to produce a solution containing 0.025% w/v of Bendroflumethiazide; shake for 10 minutes and filter.

(2) 0.1% w/v of *bendroflumethiazide BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of solution (1) and 5 µL of solution (2).

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in air, examine under *ultraviolet light (254 nm)* and then reveal the spots by *Method I*.

MOBILE PHASE

Ethyl acetate.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.6 to 3.0, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions. Store and inject the solutions at 4°, using a cooled autosampler.

(1) Add 30 mL of *methanol* to a quantity of the oral suspension containing 2.5 mg of Bendroflumethiazide and shake vigorously. Add about 10 mL of a 5% w/v solution of *sodium chloride*, allow to cool and add sufficient of the 5% w/v *sodium chloride* to produce 50 mL. Filter the resulting solution through a 0.45-µm nylon filter, discarding the first 5 mL of filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) Dilute 1 volume of solution (2) to 10 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed *with octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters SunFire C18 is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with the same material.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 20°.

(e) Use a detection wavelength of 273 nm.

(f) Inject 10 µL of each solution.

When the chromatograms are recorded under the prescribed conditions the retention time of bendroflumethiazide is about 16.5 minutes and the relative retention of impurity A [4-amino-6-(trifluoromethyl)benzene-1,3-disulfonamide] is about 0.33.

MOBILE PHASE

Mobile phase A

4 volumes of *acetonitrile* and 16 volumes of *water*; adjust the pH of the mixture to 2.0 using *orthophosphoric acid*.

Mobile phase B

4 volumes of *water* and 6 volumes of *acetonitrile*; adjust the pH of the mixture to 2.0 using *orthophosphoric acid*.

Equilibrate the column with mobile phase A for at least 1 hour before starting the elution programme.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100	0	isocratic
10-14	100→0	0→100	linear gradient
14-18	0	100	isocratic
18-22	0→100	100→0	linear gradient
22-28	100	0	re-equilibration

SYSTEM SUITABILITY

The following test applies only if a peak due to impurity A and a peak with a retention relative to that of bendroflumethiazide of about 0.24 are present.

The test is not valid unless, in the chromatogram obtained with solution (1), the *resolution* between the peak due to impurity A and the peak with a retention relative to bendroflumethiazide of about 0.24 is at least 1.5. If co-elution of these peaks occurs, re-equilibrate the column for at least 1 hour and repeat using freshly prepared mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks*, excluding the peak due to impurity A, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions. Store and inject the solutions at 4°, using a cooled autosampler.

(1) Add 30 mL of *methanol* to a weighed quantity of the oral suspension containing 2.5 mg of Bendroflumethiazide and shake vigorously. Add about 10 mL of a 5% w/v solution of *sodium chloride*, allow to cool and add sufficient of the 5% w/v *sodium chloride* to produce 50 mL. Filter the resulting solution through a 0.45-µm nylon filter, discarding the first 5 mL of filtrate.
(2) Dilute 1 volume of a 0.025% w/v solution of *bendroflumethiazide BPCRS* in *methanol* to 5 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak corresponding to bendroflumethiazide is between 0.9 and 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{15}H_{14}F_3N_3O_4S_2$, weight in volume, using the declared content of $C_{15}H_{14}F_3N_3O_4S_2$ in *bendroflumethiazide BPCRS*.

STORAGE

Bendroflumethiazide Oral Suspension should be stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Bendroflumethiazide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bendroflumethiazide Tablets

General Notices

Action and use

Thiazide diuretic.

DEFINITION

Bendroflumethiazide Tablets contain Bendroflumethiazide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bendroflumethiazide, $C_{15}H_{14}F_3N_3O_4S_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of 0.005M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

www.webofpharma.com

https://thuocngocanh.com/

(1) After 45 minutes withdraw a sample of the medium, filter (a polyethylene filter is suitable) and dilute the filtrate with sufficient of the dissolution medium, if necessary, to produce a solution expected to contain 0.00028% w/v of Bendroflumethiazide.

(2) 0.028% w/v of *bendroflumethiazide BPCRS* in *methanol*. Dilute 1 volume to 100 volumes with the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (SunFire C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 273 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes of *acetonitrile* and 60 volumes of *water*, adjusted to pH 2.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of bendroflumethiazide is about 8 minutes.

DETERMINATION OF CONTENT

Calculate the total content of bendroflumethiazide, $C_{15}H_{14}F_3N_3O_4S_2$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{14}F_3N_3O_4S_2$ in *bendroflumethiazide BPCRS*.

LIMITS

The amount of bendroflumethiazide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A. Protect the solutions from light.

(1) Shake a quantity of powdered tablets containing 12.5 mg of Bendroflumethiazide with 15 mL of *methanol*, dilute to 25 mL with mobile phase A and filter through a 0.45-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.5% w/v of *bendroflumethiazide BPCRS* and 0.005% w/v of *bendroflumethiazide impurity A EPCRS* in *methanol*. Dilute 1 volume to 10 volumes with mobile phase A.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters SunFire C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 273 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of *acetonitrile* and 80 volumes of *water*, adjusted to pH 2.0 with *orthophosphoric acid*.

Mobile phase B 40 volumes of *water* and 60 volumes of *acetonitrile*, adjusted to pH 2.0 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	100	0	isocratic
10-14	100→0	0→100	linear gradient
14-18	0	100	isocratic
18-22	0→100	100→0	linear gradient
22-28	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference bendroflumethiazide (retention time about 16 minutes) is: impurity A, about 0.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and bendroflumethiazide is at least 40.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Protect the solutions from light.

(1) Shake a quantity of powdered tablets containing 12.5 mg of Bendroflumethiazide with 30 mL of *methanol* and dilute to 50 mL with the mobile phase. Dilute 1 volume to 50 volumes with the mobile phase and filter through a 0.45-µm nylon filter.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.005% w/v of *bendroflumethiazide BPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.

(3) 0.005% w/v of *bendroflumethiazide BPCRS* and 0.0005% w/v of *bendroflumethiazide impurity A EPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and bendroflumethiazide is at least 15.

DETERMINATION OF CONTENT

Calculate the content of bendroflumethiazide, $C_{15}H_{14}F_3N_3O_4S_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{14}F_3N_3O_4S_2$ in *bendroflumethaizide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Bendroflumethiazide.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

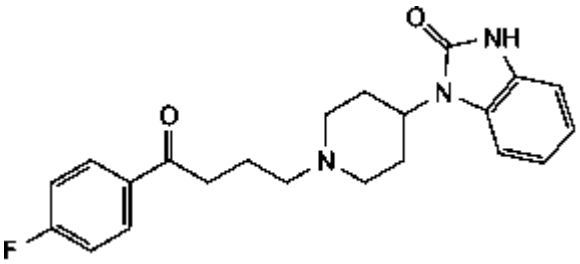
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benperidol

General Notices

(Ph. Eur. monograph 1172)



$C_{22}H_{24}FN_3O_2$ 381.4 *2062-84-2*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

1-[1-[4-(4-Fluorophenyl)-4-oxobutyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in dimethylformamide, soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison benperidol CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of methyl isobutyl ketone R, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 30 mg of the substance to be examined in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (a) Dissolve 30 mg of benperidol CRS in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (b) Dissolve 30 mg of benperidol CRS and 30 mg of droperidol CRS in the mobile phase and dilute to 10 mL with the mobile phase.

Plate TLC silica gel F_{254} plate R.

Mobile phase acetone R, methanol R (10:90 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 10 mg in 5 mL of anhydrous ethanol R. Add 0.5 mL of dinitrobenzene solution R and 0.5 mL of 2 M alcoholic potassium hydroxide R. A violet colour is produced which becomes brownish-red after 20 min.

D. Mix about 5 mg with 45 mg of heavy magnesium oxide R and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of water R, 0.05 mL of phenolphthalein solution R1 and about 1 mL of dilute hydrochloric acid R to render the solution colourless. Filter. To a freshly prepared mixture of 0.1 mL of alizarin S solution R and 0.1 mL of zirconyl nitrate solution R, add 1.0 mL of the filtrate. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.10 g of the substance to be examined in *dimethylformamide R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2.5 mg of *benperidol CRS* and 2.5 mg of *droperidol CRS* in *dimethylformamide R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *dimethylformamide R*. Dilute 5.0 mL of this solution to 20.0 mL with *dimethylformamide R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 10 g/L solution of *tetrabutylammonium hydrogen sulfate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100 → 60	0 → 40
15 - 20	60	40
20 - 25	100	0

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL.

Relative retention With reference to benperidol (retention time = about 6.5 min): impurity A = about 0.2; impurity B = about 0.9; droperidol = about 1.1; impurity D = about 1.2; impurity E = about 1.3; impurity C = about 1.5.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to benperidol and droperidol.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

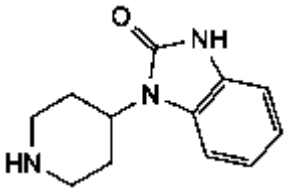
1 mL of *0.1 M perchloric acid* is equivalent to 38.14 mg of $C_{22}H_{24}FN_3O_2$.

STORAGE

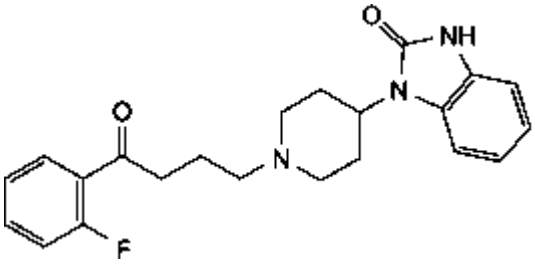
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*



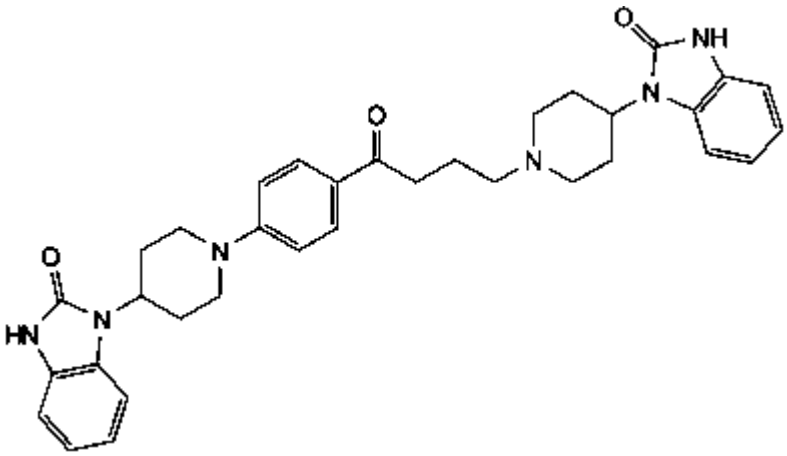
A. 1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one,



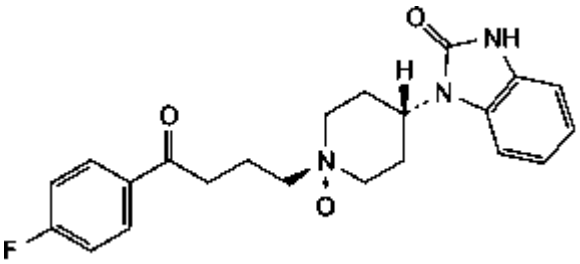
B. 1-[1-[4-(2-fluorophenyl)-4-oxobutyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one,

www.webofpharma.com

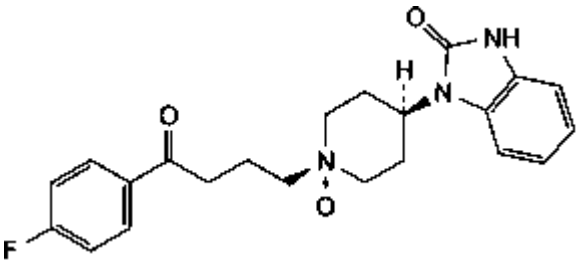
https://thuocngocanh.com/



C. 1-[1-[4-oxo-4-[4-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]phenyl]butyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one,



D. *cis*-1-[1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl 1-oxide]-1,3-dihydro-2*H*-benzimidazol-2-one,



E. *trans*-1-[1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl 1-oxide]-1,3-dihydro-2*H*-benzimidazol-2-one.

Ph Eur

© Crown Copyright 2022

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

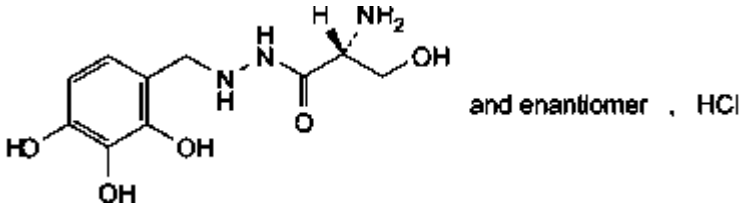
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benserazide Hydrochloride

General Notices

(Ph. Eur. monograph 1173)



and enantiomer , HCl

$C_{10}H_{16}ClN_3O_5$ 293.7 *14919-77-8*

Action and use

Dopa decarboxylase inhibitor.

Preparations

Co-beneldopa Capsules

Co-beneldopa Dispersible Tablets

Co-beneldopa Prolonged-release Capsules

Ph Eur

DEFINITION

(2*RS*)-2-Amino-3-hydroxy-*N*′-[(2,3,4-trihydroxyphenyl)methyl]propanehydrazide hydrochloride.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white or orange-white, crystalline powder.

Solubility

Freely soluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in acetone.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *benserazide hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in hot *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Dissolve 16 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

pH (2.2.3)

4.0 to 5.0 for solution S.

Related substances

Liquid chromatography (2.2.29). *All solutions must be injected immediately or stored at 4 °C.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5.0 mg of *benserazide impurity A CRS* and 5.0 mg of *benserazide impurity C CRS* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 5 mg of *benserazide for peak identification A CRS* (containing impurity B) in 5 mL of reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: dissolve 2.2 g of *sodium heptanesulfonate monohydrate R* and 6.8 g of *potassium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, add 50 mL of *methanol R2* and adjust to pH 3.5 with *phosphoric acid R*;

— *mobile phase B*: dissolve 2.2 g of *sodium heptanesulfonate monohydrate R* and 6.8 g of *potassium dihydrogen phosphate R* in 500 mL of *water for chromatography R*, adjust to pH 3.5 with *phosphoric acid R* and add 500 mL of *methanol R2*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100 → 0	0 → 100
15 - 25	0	100

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C; use the chromatogram supplied with *benserazide for peak identification A CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; doubling of the peak due to impurity C, related to separation of the (*EZ*)-isomers, may be observed.

Relative retention With reference to benserazide (retention time = about 9 min): impurity A = about 0.6; impurity C = about 1.2; impurity B = about 1.5.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to benserazide and impurity C; use the 1st peak of impurity C if 2 peaks occur.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.7;

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity C*: not more than the area of the corresponding peak or pair of peaks in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *sum of impurities other than A*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.500 g. Use as the solvent a solution containing 30 mL of *formamide R*, 30 mL of *methanol R* and 7.0 g of *salicylic acid R* (the *salicylic acid R* must be added to the solvent mixture in the titration vessel).

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating during the titration, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.250 g in 5 mL of *anhydrous formic acid R*. Add 70 mL of *anhydrous acetic acid R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

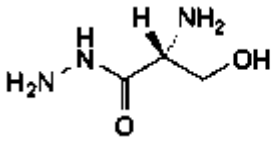
1 mL of *0.1 M perchloric acid* is equivalent to 29.37 mg of $C_{10}H_{16}ClN_3O_5$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C.*

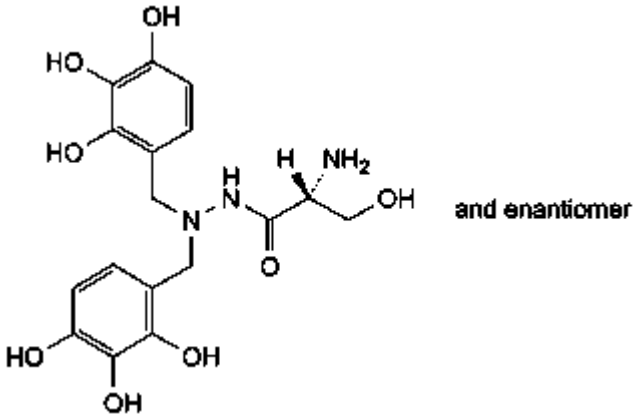


and enantiomer

A. (2*RS*)-2-amino-3-hydroxypropanehydrazide,

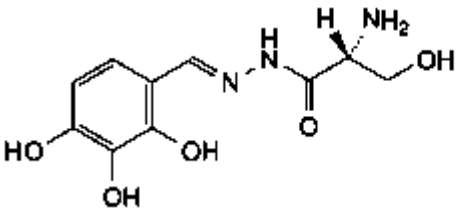
www.webofpharma.com

https://thuvienthuocngocanh.com/



and enantiomer

B. (2*RS*)-2-amino-3-hydroxy-*N*′,*N*′-bis[(2,3,4-trihydroxyphenyl)methyl]propanehydrazide,



its (*Z*)-isomer and their enantiomers

C. (2*RS*)-2-amino-3-hydroxy-*N*′-[(*EZ*)-(2,3,4-trihydroxyphenyl)methylidene]propanehydrazide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bentonite

General Notices

(Ph. Eur. monograph 0467)

Ph Eur

DEFINITION

Natural clay containing a high proportion of montmorillonite, a native hydrated aluminium silicate in which some aluminium and silicon atoms may be replaced by other atoms such as magnesium and iron.

CHARACTERS

Appearance

Very fine, homogeneous, greyish-white powder with a more or less yellowish or pinkish tint.

Solubility

Practically insoluble in water and in aqueous solutions.

It swells with a little water forming a malleable mass.

IDENTIFICATION

A. To 0.5 g in a metal crucible add 1 g of *potassium nitrate R* and 3 g of *sodium carbonate R* and heat until the mixture melts. Allow to cool. To this residue add 20 mL of boiling *water R*, mix and filter. Wash the insoluble residue with 50 mL of *water R*. To this residue add 1 mL of *hydrochloric acid R* and 5 mL of *water R*. Filter. To the filtrate add 1 mL of *strong sodium hydroxide solution R* and filter. To this filtrate add 3 mL of *ammonium chloride solution R*. A gelatinous white precipitate is formed.

B. Add 2.0 g in 20 portions to 100 mL of a 10 g/L solution of *sodium laurilsulfate R* in a 100 mL graduated cylinder about 30 mm in diameter. Allow 2 min between additions for each portion to settle. Allow to stand for 2 h. The apparent volume of the sediment is not less than 22 mL.

C. 0.25 g gives the reaction of silicates (*2.3.1*).

TESTS

Alkalinity

To 2 g add 100 mL of *carbon dioxide-free water R* and shake for 5 min. To 5 mL of this suspension add 0.1 mL of *thymolphthalein solution R*. The liquid becomes bluish. Add 0.1 mL of *0.1 M hydrochloric acid*. The liquid is decolourised within 5 min.

Coarse particles

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent.

To 20 g add 1000 mL of *water R* and mix for 15 min using a high-speed mixer capable of operating at not less than 5000 r/min. Transfer the suspension to a wet sieve (75), tared after drying at 100-105 °C. Wash with 3 quantities, each of 500 mL, of *water R*, ensuring that any agglomerates have been dispersed. Dry the sieve at 100-105 °C and weigh. The particles on the sieve weigh a maximum of 0.1 g.

Loss on drying (*2.2.32*)

Maximum 15 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for bentonite used as viscosity-increasing agent or suspending agent.

Sedimentation volume

To 6.0 g add 200 mL of *water R* and mix for 20 min using a high-speed mixer capable of operating at 10 000 r/min. Transfer 100 mL of this suspension to a graduated cylinder. Allow to stand for 24 h. The volume of the clear supernatant is not greater than 2 mL.

Swelling power with water

See Identification B.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

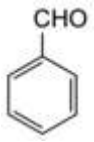
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzaldehyde

General Notices



C_7H_6O 106.1 *100-52-7*

Action and use

Flavour.

DEFINITION

Benzaldehyde contains not less than 98.0% w/w and not more than 100.5% w/w of C_7H_6O.

CHARACTERISTICS

A clear, colourless liquid.

Slightly soluble in *water*; miscible with *ethanol (96%)* and with *ether*.

TESTS

Refractive index

1.544 to 1.546, Appendix V E.

Weight per mL

1.043 to 1.049 g, Appendix V G.

Free acid

Not more than 1.0% w/v, calculated as benzoic acid, $C_7H_6O_2$, when determined by the following method. To 10 mL add 20 mL of *ethanol (96%)* previously neutralised to *phenolphthalein solution R1* and titrate with *0.1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 12.21 mg of $C_7H_6O_2$.

Chlorinated compounds

www.webofpharma.com

https://thuocngocanh.com/

Not more than 0.05% w/v, calculated as Cl, when determined by the following method. To 5 mL add 50 mL of *isoamyl alcohol* and 3 g of *sodium* and boil under a reflux condenser for 1 hour. Cool, add 50 mL of *water* and 15 mL of *nitric acid*, cool, add 5 mL of *0.1M silver nitrate VS*, shake and titrate the excess silver nitrate with *0.1M ammonium thiocyanate VS* using *ammonium iron(III) sulfate solution R2* as indicator. Repeat the procedure without the substance being examined. The difference between the titrations represents the amount of silver nitrate required. Each mL of *0.1M silver nitrate VS* is equivalent to 3.545 mg of Cl.

ASSAY

Carry out the method for *determination of aldehydes*, Appendix X K, using 0.5 g. Each mL of *0.5M potassium hydroxide in ethanol (60%) VS* is equivalent to 53.06 mg of C_7H_6O.

STORAGE

Benzaldehyde should be kept in a well-filled container, protected from light and stored at a temperature not exceeding 15°.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

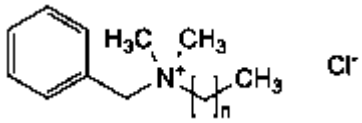
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzalkonium Chloride

General Notices

(Ph. Eur. monograph 0372)



8001-54-5

Action and use

Antiseptic.

Ph Eur

DEFINITION

Mixture of alkylbenzyldimethylammonium chlorides, the alkyl groups mainly having chain lengths of C_{12}, C_{14} and C_{16}.

Content

95.0 per cent to 104.0 per cent of alkylbenzyldimethylammonium chlorides (anhydrous substance) calculated using the average relative molecular mass (see Tests).

CHARACTERS

Appearance

White or yellowish-white powder or gelatinous, yellowish-white fragments, hygroscopic. On heating it forms a clear molten mass.

Solubility

Very soluble in water and in ethanol (96 per cent). An aqueous solution froths copiously when shaken.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

www.webofpharma.com

https://thuvienthuocngocanh.com/

Test solution Dissolve 80 mg in *water R* and dilute to 100.0 mL with the same solvent.

Spectral range 220-350 nm.

Absorption maxima At 257 nm, 263 nm and 269 nm.

Shoulder At about 250 nm.

B. Examine the chromatograms obtained in the test for average relative molecular mass and ratio of alkyl components.

Results The principal peaks in the chromatogram obtained with the test solution are similar in retention time to the principal peaks in the chromatogram obtained with the reference solution.

C. To 2 mL of solution S (see Tests) add 0.1 mL of *glacial acetic acid R* and, dropwise, 1 mL of *sodium tetraphenylborate solution R*. A white precipitate is formed. Filter. Dissolve the precipitate in a mixture of 1 mL of *acetone R* and 5 mL of *ethanol (96 per cent) R*, heating to not more than 70 °C. Add *water R* dropwise to the warm solution until a slight opalescence forms. Heat gently until the solution is clear and allow to cool. White crystals separate. Filter, wash with 3 quantities, each of 10 mL, of *water R* and dry *in vacuo* (*2.2.32*) at a temperature not exceeding 50 °C. The crystals melt (*2.2.14*) at 127 °C to 133 °C.

D. To 5 mL of *dilute sodium hydroxide solution R* add 0.1 mL of *bromophenol blue solution R1* and 5 mL of *methylene chloride R* and shake. The methylene chloride layer is colourless. Add 0.1 mL of solution S and shake. The methylene chloride layer becomes blue.

E. To 2 mL of solution S add 1 mL of *dilute nitric acid R*. A white precipitate is formed which dissolves on the addition of 5 mL of *ethanol (96 per cent) R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 50 mL of solution S add 0.1 mL of *bromocresol purple solution R*. Not more than 0.1 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Average relative molecular mass and ratio of alkyl components

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.400 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution Dissolve the contents of a vial of *benzalkonium chloride for system suitability CRS* in 5 mL of *water R*.

Column:

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped cyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 45 volumes of *acetonitrile R* and 55 volumes of a 13.6 g/L solution of *sodium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of homologues Use the chromatogram supplied with *benzalkonium chloride for system suitability CRS* and the chromatogram obtained with the reference solution to identify the peaks due to C_{12}, C_{14} and C_{16}.

Relative retention With reference to C_{12} homologue (retention time = about 6 min): C_{14} homologue = about 1.3; C_{16} homologue = about 1.7.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to the C_{12} and C_{14} homologues.

Calculate the average relative molecular mass of the sample by summing the products for each homologue, using the following expression:

$$W\left(\frac{A}{B}\right)$$

A	=	area of the peak due to the given homologue in the chromatogram obtained with the test solution;
B	=	sum of the areas of the peaks due to all homologues in the chromatogram obtained with the test solution;
W	=	relative molecular mass for the given homologue: 340, 368 and 396 for the C_{12}, C_{14} and C_{16} homologues, respectively.

Calculate the percentage of each homologue, using the following expression:

$$100\left(\frac{C}{D}\right)$$

C	=	product of the relative molecular mass of the given homologue and the area of the corresponding peak in the chromatogram obtained with the test solution;
D	=	sum of the *C* values for all homologues quantified.

Limits:

— *C_{12} homologue*: minimum 40 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *C_{14} homologue*: minimum 20 per cent;

— *sum of C_{12} and C_{14} homologues*: minimum 70 per cent.

Impurities A, B and C

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 0.500 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 25.0 mg of *benzyl alcohol CRS* (impurity A) in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 75.0 mg of *benzaldehyde CRS* (impurity B) in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dilute 1 mL of reference solution (a) to 10 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.09 g of *sodium hexanesulfonate R* and 6.9 g of *sodium dihydrogen phosphate monohydrate R* in *water for chromatography R*; adjust to pH 3.5 with *phosphoric acid R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: *methanol R2*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	80	20
10 - 14	80 → 50	20 → 50
14 - 35	50	50
35 - 36	50 → 20	50 → 80
36 - 55	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm for impurities A and C, and at 257 nm for impurity B.

Injection 20 µL.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to impurity A (retention time = about 10 min): impurity B = about 1.3; impurity C = about 2.4.

System suitability At 210 nm:

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (c);

— *symmetry factor*: minimum 0.6 for the peak due to impurity A in the chromatogram obtained with reference solution (a).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.3;

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurity C*: not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Amines and amine salts

Dissolve 5.0 g with heating in 20 mL of a mixture of 3 volumes of *1 M hydrochloric acid* and 97 volumes of *methanol R* and add 100 mL of *2-propanol R*. Pass a stream of *nitrogen R* slowly through the solution. Titrate with up to 12.0 mL of *0.1 M tetrabutylammonium hydroxide* and record the potentiometric titration curve (*2.2.20*). If the curve shows 2 points of inflexion, the volume of titrant added between the 2 points is not greater than 5.0 mL. If the curve shows no point of inflexion, the substance to be examined does not comply with the test. If the curve shows 1 point of inflexion, repeat the test but add 3.0 mL of a 25.0 g/L solution of *dimethyldecylamine R* in *2-propanol R* before the titration. If the titration curve after addition of 12.0 mL of the titrant shows only 1 point of inflexion, the substance to be examined does not comply with the test.

Water (*2.5.12*)

Maximum 10 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 2.00 g in *water R* and dilute to 100.0 mL with the same solvent. Transfer 25.0 mL of the solution to a separating funnel, add 25 mL of *methylene chloride R*, 10 mL of *0.1 M sodium hydroxide* and 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R*. Shake well, allow to separate and discard the methylene chloride layer. Shake the aqueous layer with 3 quantities, each of 10 mL, of *methylene chloride R* and discard the methylene chloride layers. To the aqueous layer add 40 mL of *hydrochloric acid R*, allow to cool and titrate with *0.05 M potassium iodate* until the deep-brown colour is almost discharged. Add 5 mL of *methylene chloride R* and continue the titration,

www.webofpharma.com

https://thuvienthuocngocanh.com/

shaking vigorously, until the methylene chloride layer no longer changes colour. Carry out a blank titration on a mixture of 10.0 mL of the freshly prepared 50 g/L solution of *potassium iodide R*, 20 mL of *water R* and 40 mL of *hydrochloric acid R*.

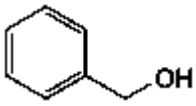
1 mL of *0.05 M potassium iodate* is equivalent to $\frac{x}{10}$ mg of benzalkonium chloride where *x* is the average relative molecular mass of the sample.

STORAGE

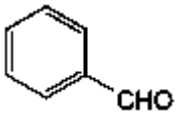
In an airtight container.

IMPURITIES

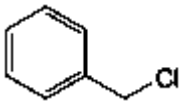
Specified impurities *A, B, C.*



A. benzyl alcohol,



B. benzaldehyde,



C. (chloromethyl)benzene.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzalkonium Chloride Solution

General Notices

(Ph. Eur. monograph 0371)

Action and use

Antiseptic.

Ph Eur

DEFINITION

Aqueous solution of a mixture of alkylbenzyldimethylammonium chlorides, the alkyl groups mainly having chain lengths of C_{12}, C_{14} and C_{16}.

Content

475 g/L to 525 g/L of alkylbenzyldimethylammonium chlorides, calculated using the average relative molecular mass (see Tests). The solution may contain ethanol (96 per cent).

CHARACTERS

Appearance

Clear, colourless or slightly yellowish liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

It froths copiously when shaken.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution Dilute 0.3 mL to 100.0 mL with *water R*.

Spectral range 220-350 nm.

www.webofpharma.com

https://thuocngocanh.com/

Absorption maxima At 257 nm, 263 nm and 269 nm.

Shoulder At about 250 nm.

B. Examine the chromatograms obtained in the test for average relative molecular mass and ratio of alkyl components.

Results The principal peaks in the chromatogram obtained with the test solution are similar in retention time to the principal peaks in the chromatogram obtained with the reference solution.

C. To 0.05 mL add 2 mL of *water R*, 0.1 mL of *glacial acetic acid R* and, dropwise, 1 mL of *sodium tetraphenylborate solution R*. A white precipitate is formed. Filter. Dissolve the precipitate in a mixture of 1 mL of *acetone R* and 5 mL of *ethanol (96 per cent) R*, heating to not more than 70 °C. Add *water R* dropwise to the warm solution until a slight opalescence forms. Heat gently until the solution is clear and allow to cool. White crystals separate. Filter, wash with 3 quantities, each of 10 mL, of *water R* and dry *in vacuo* (2.2.32) at a temperature not exceeding 50 °C. The crystals melt (2.2.14) at 127 °C to 133 °C.

D. To 5 mL of *dilute sodium hydroxide solution R* add 0.1 mL of *bromophenol blue solution R1* and 5 mL of *methylene chloride R* and shake. The methylene chloride layer is colourless. Add 0.05 mL of the solution to be examined and shake. The methylene chloride layer becomes blue.

E. To 0.05 mL add 1 mL of *dilute nitric acid R*. A white precipitate is formed which dissolves on the addition of 5 mL of *ethanol (96 per cent) R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dilute 2.0 g to 100 mL with *carbon dioxide-free water R*.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Acidity or alkalinity

To 50 mL of solution S add 0.1 mL of *bromocresol purple solution R*. Not more than 0.1 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Average relative molecular mass and ratio of alkyl components

Liquid chromatography (2.2.29).

Test solution Determine the density (2.2.5) of the solution to be examined. Dilute a quantity of the solution to be examined equivalent to about 0.400 g of benzalkonium chloride to 100.0 mL with *water R*.

Reference solution Dissolve the contents of a vial of *benzalkonium chloride for system suitability CRS* in 5 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *end-capped cyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 45 volumes of *acetonitrile R* and 55 volumes of a 13.6 g/L solution of *sodium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of homologues Use the chromatogram supplied with *benzalkonium chloride for system suitability CRS* and the chromatogram obtained with the reference solution to identify the peaks due to homologues C_{12}, C_{14} and C_{16}.

Relative retention With reference to C_{12} homologue (retention time = about 6 min): C_{14} homologue = about 1.3; C_{16} homologue = about 1.7.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to the C_{12} and C_{14} homologues.

Calculate the average relative molecular mass of the sample by summing the products for each homologue, using the following expression:

$$W\left(\frac{A}{B}\right)$$

A	=	area of the peak due to the given homologue in the chromatogram obtained with the test solution;
B	=	sum of the areas of the peaks due to all homologues in the chromatogram obtained with the test solution;
W	=	relative molecular mass for the given homologue: 340, 368 and 396 for the C_{12}, C_{14} and C_{16} homologues, respectively.

Calculate the percentage of each homologue, using the following expression:

$$100\left(\frac{C}{D}\right)$$

C	=	product of the relative molecular mass of the given homologue and the area of the corresponding peak in the chromatogram obtained with the test solution;
D	=	sum of the *C* values for all homologues quantified.

Limits:

— *C_{12} homologue*: minimum 40 per cent;

— *C_{14} homologue*: minimum 20 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *sum of C_{12} and C_{14} homologues*: minimum 70 per cent.

Impurities A, B and C

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Determine the density (2.2.5) of the solution to be examined. Dilute a quantity of the solution to be examined equivalent to 2.5 g of benzalkonium chloride to 50.0 mL with *methanol R*.

Reference solution (a) Dissolve 25.0 mg of *benzyl alcohol CRS* (impurity A) in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 75.0 mg of *benzaldehyde CRS* (impurity B) in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dilute 1 mL of reference solution (a) to 10 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.09 g of *sodium hexanesulfonate R* and 6.9 g of *sodium dihydrogen phosphate monohydrate R* in *water for chromatography R*; adjust to pH 3.5 with *phosphoric acid R* and dilute to 1000 mL with the same solvent;

— *mobile phase B*: *methanol R2*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	80	20
10 - 14	80 → 50	20 → 50
14 - 35	50	50
35 - 36	50 → 20	50 → 80
36 - 55	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm for impurities A and C, and at 257 nm for impurity B.

Injection 20 µL.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to impurity A (retention time = about 10 min): impurity B = about 1.3; impurity C = about 2.4.

System suitability At 210 nm:

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (c);

— *symmetry factor*: minimum 0.6 for the peak due to impurity A in the chromatogram obtained with reference solution (a).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.3;

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurity C*: not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Amines and amine salts

Mix 10.0 g, while heating, with 20 mL of a mixture of 3 volumes of *1 M hydrochloric acid* and 97 volumes of *methanol R* and add 100 mL of *2-propanol R*. Pass a stream of *nitrogen R* slowly through the solution. Titrate with up to 12.0 mL of *0.1 M tetrabutylammonium hydroxide* and record the potentiometric titration curve (*2.2.20*). If the curve shows 2 points of inflexion, the volume of titrant added between the 2 points is not greater than 5.0 mL. If the curve shows no point of inflexion, the solution to be examined does not comply with the test. If the curve shows 1 point of inflexion, repeat the test but add 3.0 mL of a 25.0 g/L solution of *dimethyldecylamine R* in *2-propanol R* before the titration. If the titration curve after the addition of 12.0 mL of the titrant shows only 1 point of inflexion, the solution to be examined does not comply with the test.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Determine the density (*2.2.5*) of the solution to be examined. Dilute 4.00 g to 100.0 mL with *water R*. Transfer 25.0 mL of the solution to a separating funnel, add 25 mL of *methylene chloride R*, 10 mL of *0.1 M sodium hydroxide* and 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R*. Shake well, allow to separate and discard the methylene chloride layer. Shake the aqueous layer with 3 quantities, each of 10 mL, of *methylene chloride R* and discard the methylene chloride layers. To the aqueous layer add 40 mL of *hydrochloric acid R*, allow to cool and titrate with *0.05 M potassium iodate* until the deep-brown colour is almost discharged. Add 5 mL of *methylene chloride R* and continue the titration, shaking vigorously, until the methylene chloride layer no longer changes colour. Carry out a blank titration on a mixture of 10.0 mL of the freshly prepared 50 g/L solution of *potassium iodide R*, 20 mL of *water R* and 40 mL of *hydrochloric acid R*.

1 mL of *0.05 M potassium iodate* is equivalent to $\frac{x}{10}$ mg of benzalkonium chloride where *x* is the average relative molecular mass of the sample.

www.webofpharma.com

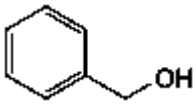
https://thuocngocanh.com/

LABELLING

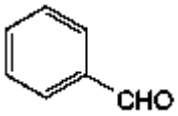
The label states the content of ethanol (96 per cent), if any.

IMPURITIES

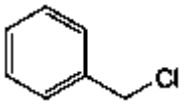
Specified impurities *A, B, C.*



A. benzyl alcohol,



B. benzaldehyde,



C. (chloromethyl)benzene.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

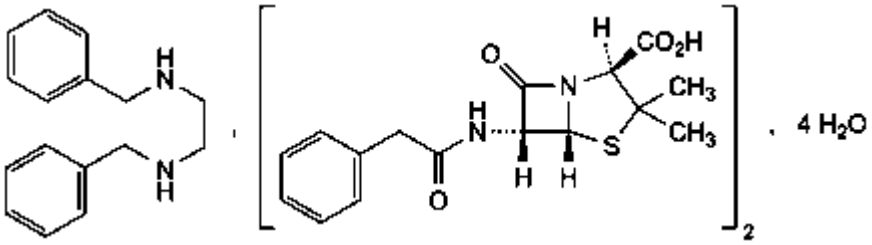
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzathine Benzylpenicillin Tetrahydrate

General Notices

Benzathine Benzylpenicillin

(Benzylpenicillin (Benzathine) Tetrahydrate, Ph. Eur. monograph 0373)



$C_{48}H_{56}N_6O_8S_2,4H_2O$ 981 *41372-02-5*

Action and use

Penicillin antibacterial.

Ph Eur

DEFINITION

N[1],*N*[2]-Dibenzylethane-1,2-diamine bis[(2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] tetrahydrate.

Salt obtained from *Benzylpenicillin sodium (0114)* or *Benzylpenicillin potassium (0113)* produced by the growth of certain strains of *Penicillium notatum* or related micro-organisms.

Content

— *benzathine benzylpenicillin*: 94.5 per cent to 102.0 per cent (anhydrous substance) without correction for dispersing or suspending agents;

— *benzathine*: 24.0 per cent to 27.0 per cent (anhydrous substance).

Dispersing or suspending agents (e.g. lecithin and polysorbate 80) may be added.

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, slightly hygroscopic powder.

Solubility

Very slightly soluble in water, freely soluble in dimethylformamide and in formamide, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *benzathine benzylpenicillin CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *methanol R*.

Reference solution Dissolve 25 mg of *benzathine benzylpenicillin CRS* in 5 mL of *methanol R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* previously adjusted to pH 7.0 with *ammonia R*.

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution:

— the chromatogram shows 2 clearly separated spots.

Results The 2 principal spots in the chromatogram obtained with the test solution are similar in position, colour and size to the 2 principal spots in the chromatogram obtained with the reference solution.

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube on a water-bath for 1 min; a reddish-brown colour develops.

D. To 0.1 g add 2 mL of *1 M sodium hydroxide* and shake for 2 min. Shake the mixture with 2 quantities, each of 3 mL, of *ether R*. Evaporate the combined ether layers to dryness and dissolve the residue in 1 mL of *ethanol (50 per cent V/V) R*. Add 5 mL of *picric acid solution R*, heat at 90 °C for 5 min and allow to cool slowly. Separate the crystals and recrystallise from *ethanol (25 per cent V/V) R* containing 10 g/L of *picric acid R*. The crystals melt (*2.2.14*) at about 214 °C.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acidity or alkalinity

To 0.50 g add 100 mL of *carbon dioxide-free water R* and shake for 5 min. Filter through a sintered-glass filter (2.1.2). To 20 mL of the filtrate add 0.1 mL of *bromothymol blue solution R1*. The solution is green or yellow. Not more than 0.2 mL of *0.02 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and by diluting to volume immediately after dissolution.*

Solution A Prepare a solution containing 1.3 g/L of *disodium hydrogen phosphate dodecahydrate R* and 6.8 g/L of *potassium dihydrogen phosphate R*.

Test solution (a) Dissolve 40.0 mg of the substance to be examined in 50 mL of *methanol R* and dilute to 100.0 mL with solution A.

Test solution (b) Dissolve 70.0 mg of the substance to be examined in 25 mL of *methanol R* and dilute to 50.0 mL with solution A.

Reference solution (a) Dissolve 40.0 mg of *benzathine benzylpenicillin CRS* in 50 mL of *methanol R* and dilute to 100.0 mL with solution A.

Reference solution (b) Dissolve 3 mg of *benzathine benzylpenicillin for peak identification CRS* (containing impurities A, B, C, D, E, F, G, H, I, J and K) in 1 mL of *methanol R* and dilute to 2 mL with solution A.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 20.0 mL with a mixture of equal volumes of *methanol R* and solution A.

Reference solution (d) Dilute 3.0 mL of reference solution (c) to 100.0 mL with a mixture of equal volumes of *methanol R* and solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 10 volumes of a 34 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.3 with *phosphoric acid R*, 30 volumes of *methanol R1* and 60 volumes of *water for chromatography R*;

— *mobile phase B*: mix 5 volumes of a 34 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.3 with *phosphoric acid R*, 25 volumes of *water for chromatography R* and 70 volumes of *methanol R1*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 16	85 → 0	15 → 100
16 - 26	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (b) and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *benzathine benzylpenicillin for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D, E, F, G, H, I, J and K.

Relative retention With reference to benzylpenicillin (retention time = about 7 min): impurity A = about 0.18; benzathine = about 0.30; impurity D = about 0.36; impurity G = about 0.38; impurity J = about 0.44; impurity E = about 0.51 and 0.60; impurity B = about 0.69; impurity F = about 0.84 and 0.88; impurity H = about 1.22; impurity I = about 1.42; impurity C = about 1.75; impurity K = about 2.90.

System suitability:

— *resolution*: minimum 1.0 between the peaks due to the epimers of impurity F and minimum 1.5 between the peaks due to impurities D and G in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 1.9; impurity F = 1.5;

— for each impurity, use the concentration of benzylpenicillin in reference solution (c).

Limits:

— *impurity C*: maximum 2.0 per cent;

— *impurity K*: maximum 1.0 per cent;

— *impurity J*: maximum 0.5 per cent;

— *impurities E (sum of isomers), F (sum of epimers)*: for each impurity, maximum 0.3 per cent;

— *impurities A, B, D, G, H, I*: for each impurity, maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.2 per cent;

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *total*: maximum 3.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to benzathine.

Water (2.5.12)

5.0 per cent to 8.0 per cent, determined on 0.200 g.

Bacterial endotoxins (2.6.14, Method E)

Less than 0.13 IU/mL, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

Suspend 20 mg in 20 mL of a solution of *0.1 M sodium hydroxide* diluted 1 to 100, shake thoroughly and centrifuge. Examine the supernatant.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (15:85 *V/V*).

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: maximum 1.8 for the peak due to benzylpenicillin.

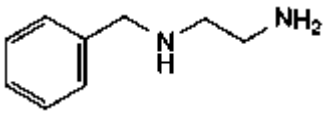
Calculate the percentage contents of benzathine ($C_{16}H_{20}N_2$) and benzathine benzylpenicillin ($C_{48}H_{56}N_6O_8S_2$) taking into account the assigned content of *benzathine benzylpenicillin CRS*.

STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

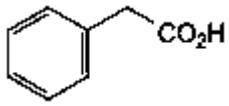
Specified impurities *A, B, C, D, E, F, G, H, I, J, K.*



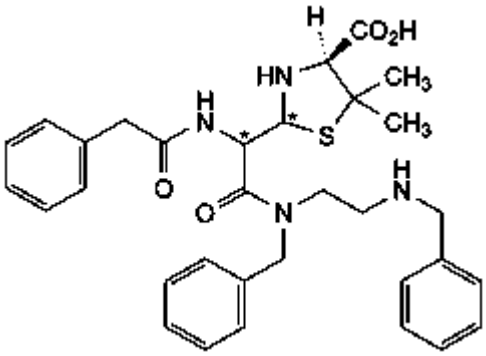
A. N^1-benzylethane-1,2-diamine,

www.webofpharma.com

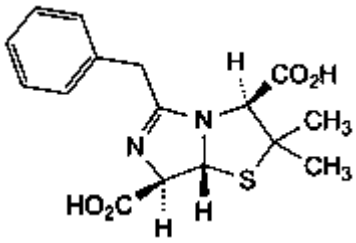
https://thuocngocanh.com/



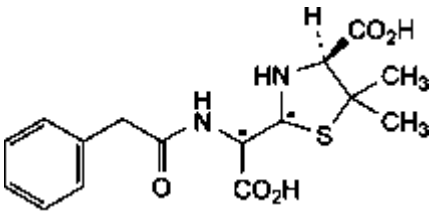
B. phenylacetic acid,



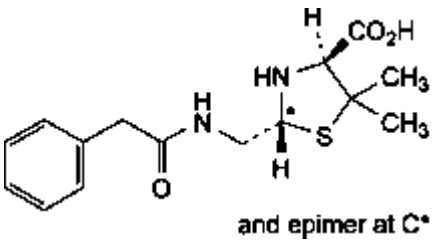
C. (2Ξ,4*S*)-2-[(1Ξ)-2-[benzyl[2-(benzylamino)ethyl]amino]-2-oxo-1-(2-phenylacetamido)ethyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (benzylpenicilloic acids benzathide),



D. (3*S*,7*R*,7a*R*)-5-benzyl-2,2-dimethyl-2,3,7,7a-tetrahydroimidazo[5,1-*b*][1,3]thiazole-3,7-dicarboxylic acid (penillic acid of benzylpenicillin),



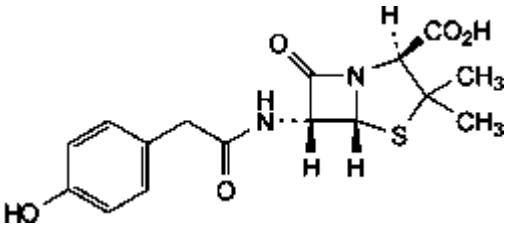
E. (2Ξ,4*S*)-2-[(Ξ)-carboxy(2-phenylacetamido)methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of benzylpenicillin),



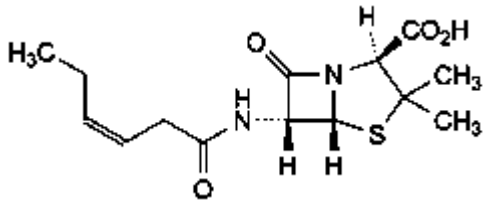
F. (2*RS*,4*S*)-5,5-dimethyl-2-[(2-phenylacetamido)methyl]-1,3-thiazolidine-4-carboxylic acid (penilloic acids of benzylpenicillin),

www.webofpharma.com

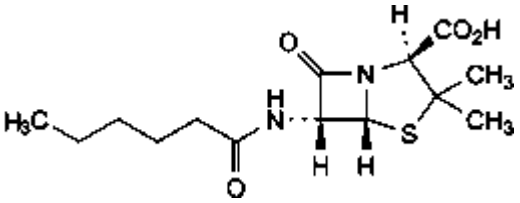
https://thuocngocanh.com/



G. (2*S*,5*R*,6*R*)-6-[2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,

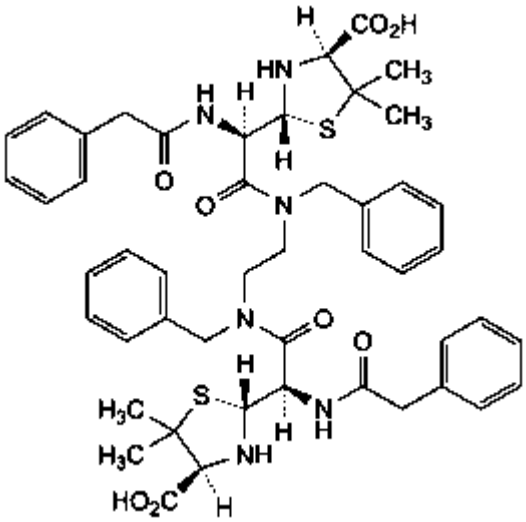


H. (2*S*,5*R*,6*R*)-6-[(3*Z*)-hex-3-enamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (isopenicillin F),



I. (2*S*,5*R*,6*R*)-6-hexanamido-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (dihydropenicillin F),

J. unknown structure,



K. (2*R*,2′*R*,4*S*,4′*S*)-2,2′-[(4*R*,11*R*)-6,9-dibenzyl-2,5,10,13-tetraoxo-1,14-diphenyl-3,6,9,12-tetraazatetradecane-4,11-diyl]bis(5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid).

Ph Eur

© Crown Copyright 2022

https://thuocngocanh.com/

Medicines & Healthcare products
Regulatory Agency

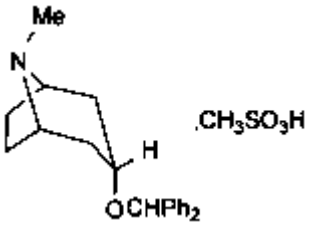
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzatropine Mesilate

General Notices



$C_{21}H_{25}NO,CH_4O_3S$ 403.5 *132-17-2*

Action and use

Anticholinergic.

Preparations

Benzatropine Injection

Benzatropine Tablets

DEFINITION

Benzatropine Mesilate is (1*R*,3*R*,5*S*)-3-benzhydryloxytropane methanesulfonate. It contains not less than 98.0% and not more than 100.5% of $C_{21}H_{25}NO,CH_4O_3S$, calculated with reference to the dried substance.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

CHARACTERISTICS

A white, crystalline powder. It melts at about 144°.

Very soluble in *water*; freely soluble in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Dry the substance at 105° for 3 hours. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of benzatropine mesilate (*RS 026*).

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.1% w/v solution in *2M hydrochloric acid* exhibits two maxima, at 253 and 258 nm. The *absorbance* at 253 nm is about 0.96 and at 258 nm is about 1.1.

C. Dissolve 10 mg in 2 mL of *water*, pour into 5 mL of hot *picric acid solution R1* and allow to cool. The *melting point* of the precipitate, after drying at 105°, is about 185°, Appendix V A.

TESTS

Tropine

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 75 volumes of *ethanol (96%)* and 15 volumes of *13.5M ammonia* as the mobile phase. Apply separately to the plate 10 µL of each of two solutions in *acetone* containing (1) 4.0% w/v of the substance being examined and (2) 0.020% w/v of *tropine*. After removal of the plate, allow it to dry in air and spray with *sodium iodobismuthate solution* and then with a 0.4% w/v solution of *sulfuric acid*. Any spot corresponding to tropine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) mix with the aid of ultrasound 50 mg of the substance being examined with 15 mL of mobile phase A, dilute to 50 mL with the same solvent and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes with mobile phase A and further dilute 1 volume of the resulting solution to 5 volumes with the same solvent. For solution (3) mix with the aid of ultrasound 50 mg of *desmethyl benzatropine hydrochloride BPCRS* with 15 mL of mobile phase A, dilute to 100 mL and dilute 1 volume of the resulting solution to 100 volumes with the same solvent. Solution (4) contains 0.01% w/v each of *benzatropine mesilate BPCRS* and *desmethyl benzatropine hydrochloride BPCRS* in mobile phase A.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-Phenyl 5µ is suitable). Carry out a linear gradient elution with a flow rate of 1 mL per minute using the following conditions. Use a detection wavelength of 220 nm.

Mobile phase A A mixture of 5 volumes of a 1M potassium phosphate buffer prepared as described for mobile phase B, 20 volumes of *acetonitrile* and 75 volumes of *water*.

Mobile phase B A mixture of 35 volumes of *water*, 60 volumes of *acetonitrile* and 5 volumes of a 1M potassium phosphate buffer prepared in the following manner: dissolve 136.1 g of *potassium dihydrogen orthophosphate* in 900 mL of *water*, add 5 mL of *orthophosphoric acid (85%)* and dilute to 1000 mL.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	70→30	30→70	linear gradient
20-30	30→0	70→100	linear gradient
30-55	0	100	isocratic
55-65	70	30	isocratic

Inject 20 µL of solution (4). The test is not valid unless the *resolution factor* between the two principal peaks is at least 1. If necessary adjust the concentration of *acetonitrile* or adjust the time program of the linear gradient elution.

Inject separately 20 µL of mobile phase A as a blank and 20 µL each of solutions (1), (2) and (3). In the chromatogram obtained with solution (1) the area of any peak corresponding to desmethyl benzatropine is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%), the area of any other *secondary peak* is not greater that the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and the sum of the areas of any such peaks is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). In solution (1) disregard any peaks corresponding to the peaks in the chromatogram obtained with the blank solution.

Loss on drying

When dried to constant weight at 105°, loses not more than 5.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 0.6 g in 25 mL of *water*, add 5 mL of *dilute sodium carbonate solution* and extract with four 10 mL quantities of *chloroform*. Wash the combined extracts with 10 mL of *water*, extract the washings with 5 mL of *chloroform* and add the chloroform to the combined extracts. Filter and wash the filter with 5 mL of *chloroform*. To the combined filtrate and washings add 25 mL of *1,4-dioxan* and titrate with *0.1M perchloric acid VS* using 0.15 mL of a 0.1% w/v solution of *methyl red* in *methanol* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 40.35 mg of $C_{21}H_{25}NO,CH_4O_3S$.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzatropine Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Benzatropine Tablets contain Benzatropine Mesilate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

Content of benzatropine mesilate, $C_{21}H_{25}NO,CH_4O_3S$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a suitable quantity of the powdered tablets with *2M hydrochloric acid* and filter. Dilute the filtrate with sufficient *2M hydrochloric acid* to produce a solution containing 0.1% w/v of Benzatropine Mesilate. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 253 nm and 258 nm.

B. Extract a quantity of the powdered tablets containing 10 mg of Benzatropine Mesilate with 10 mL of *ethanol (96%)* and filter. Evaporate the filtrate to about 2 mL, pour into 5 mL of hot *picric acid solution R1* and allow to cool. The *melting point* of the precipitate, after drying at 105°, is about 185°, Appendix V A.

TESTS

Tropine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Benzatropine Mesilate with 4 mL of *acetone* for 5 minutes, centrifuge, evaporate 2 mL of the supernatant liquid to dryness and dissolve the residue in 0.5 mL of *acetone*.

(2) 0.010% w/v of *tropine* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *sodium iodobismuthate solution* and then with a 0.4% w/v solution of *sulfuric acid*.

MOBILE PHASE

15 volumes of 13.5M *ammonia* and 75 volumes of *ethanol (96%)*.

LIMITS

Any spot corresponding to tropine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Benzatropine Mesilate comply with the requirement stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake one tablet with 8 mL of the mobile phase for 5 minutes, add sufficient of the mobile phase to produce 10 mL, centrifuge for 5 minutes and use the supernatant liquid.

(2) 0.02% w/v of *benzatropine mesilate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (10 µm) (Lichrosorb RP8 or Spherisorb C8 is suitable).

(b) Use isocratic elution (or gradient elution) and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 259 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of *octylamine phosphate buffer pH 3.0* and 65 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{25}NO,CH_4O_3S$ in each tablet using the declared content of $C_{21}H_{25}NO,CH_4O_3S$ in *benzatropine mesilate BPCRS*.

ASSAY

Weigh and powder 30 tablets. To a quantity of the powder containing 50 mg of Benzatropine Mesilate add 50 mL of *water* and shake for 15 minutes. Add 10 mL of a 50% w/v solution of *sodium hydroxide* and an excess of *sodium chloride* and extract with successive quantities of

www.webofpharma.com

https://thuocngocanh.com/

50, 25, 25 and 25 mL of *ether*. Extract the combined ether layers with successive quantities of 25, 25, 25 and 15 mL of *2M hydrochloric acid*, dilute the combined extracts to 100 mL with *2M hydrochloric acid*, mix and filter if necessary. Measure the *absorbance* of the resulting solution at the maximum at 258 nm, Appendix II B. Calculate the content of $C_{21}H_{25}NO,CH_4O_3S$ from the *absorbance* obtained by repeating the operation using 50 mg of *benzatropine mesilate BPCRS* in place of the powdered tablets and from the declared content of $C_{21}H_{25}NO,CH_4O_3S$ in *benzatropine mesilate BPCRS*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

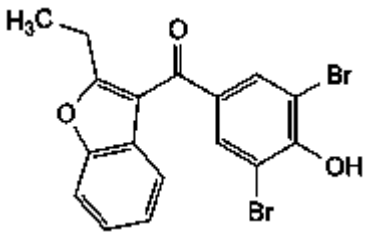
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzbromarone

General Notices

(Ph. Eur. monograph 1393)



$C_{17}H_{12}Br_2O_3$ 424.1 *3562-84-3*

Action and use

Uricosuric; treatment of hyperuricaemia.

Ph Eur

DEFINITION

(3,5-Dibromo-4-hydroxyphenyl)(2-ethylbenzofuran-3-yl)methanone.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in ethanol (96 per cent).

mp

About 152 °C.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison benzbromarone CRS.

B. By means of a copper wire, previously ignited, introduce a small amount of the substance to be examined into the non-luminous part of a flame. The colour of the flame becomes green.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, Method II).

Dissolve 1.25 g in dimethylformamide R and dilute to 25 mL with the same solvent.

Acidity or alkalinity

Shake 0.5 g with 10 mL of carbon dioxide-free water R for 1 min and filter. To 2.0 mL of the filtrate add 0.1 mL of methyl red solution R and 0.1 mL of 0.01 M hydrochloric acid. The solution is red. Add 0.3 mL of 0.01 M sodium hydroxide. The solution is yellow.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.125 g of the substance to be examined in 30 mL of methanol R and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of benzarone CRS (impurity C) in the mobile phase and dilute to 20 mL with the mobile phase. To 5 mL of this solution add 1 mL of the test solution and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase glacial acetic acid R, acetonitrile R, water R, methanol R (5:25:300:990 *V/V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 231 nm.

Injection 20 µL.

Run time 2.5 times the retention time of benzbromarone.

Relative retention With reference to benzbromarone: impurity A = about 0.6; impurity B = about 2.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (b):

— *resolution*: minimum 10.0 between the peaks due to impurity C (1st peak) and benzbromarone (2nd peak).

Limits:

— *impurity A*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurity B*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than A and B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Halides expressed as chlorides (2.4.4)

Maximum 400 ppm.

Shake 1.25 g with a mixture of 5 mL of *dilute nitric acid R* and 15 mL of *water R*. Filter. Rinse the filter with *water R* and dilute the filtrate to 25 mL with the same solvent. Dilute 2.5 mL of this solution to 15 mL with *water R*.

Iron (2.4.9)

Maximum 125 ppm.

Moisten the residue obtained in the test for sulfated ash with 2 mL of *hydrochloric acid R* and evaporate to dryness on a water-bath. Add 0.05 mL of *hydrochloric acid R* and 10 mL of *water R*, heat to boiling and maintain boiling for 1 min. Allow to cool. Rinse the crucible with *water R*, collect the rinsings and dilute to 25 mL with *water R*. Dilute 2 mL of this solution to 10 mL with *water R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 50 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 60 mL of *methanol R*. Stir until completely dissolved and add 10 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

www.webofpharma.com

https://thuvienthuocngocanh.com/

1 mL of *0.1 M sodium hydroxide* is equivalent to 42.41 mg of $C_{17}H_{12}Br_2O_3$.

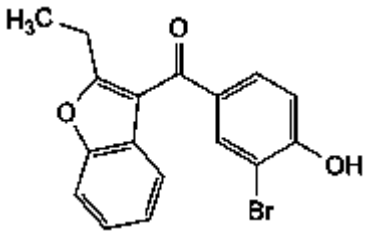
STORAGE

Protected from light.

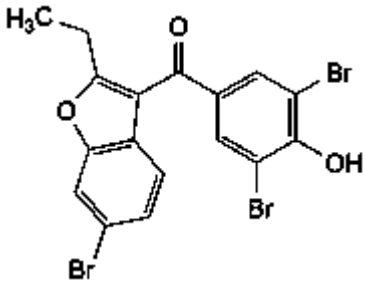
IMPURITIES

Specified impurities A, B.

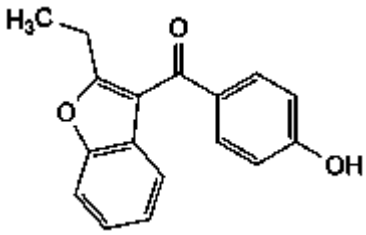
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



A. (3-bromo-4-hydroxyphenyl)(2-ethylbenzofuran-3-yl)methanone,



B. (6-bromo-2-ethylbenzofuran-3-yl)(3,5-dibromo-4-hydroxyphenyl)methanone,



C. (2-ethylbenzofuran-3-yl)(4-hydroxyphenyl)methanone (benzarone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

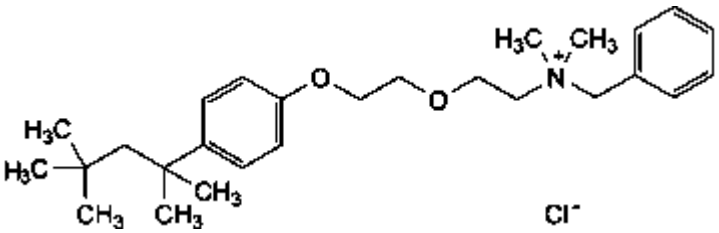
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzethonium Chloride

General Notices

(Ph. Eur. monograph 0974)



$C_{27}H_{42}ClNO_2$ 448.1 *121-54-0*

Action and use

Antiseptic.

Ph Eur

DEFINITION

N-Benzyl-*N*,*N*-dimethyl-2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethanaminium chloride.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Very soluble in water and in ethanol (96 per cent), freely soluble in methylene chloride.

An aqueous solution froths copiously when shaken.

IDENTIFICATION

A. Melting point (2.2.14): 158 °C to 164 °C, after drying at 105 °C for 4 h.

B. Thin-layer chromatography (2.2.27).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 25 mg of *benzethonium chloride CRS* in *water R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *methanol R* (5:5:100 *V/V/V*).

Application 20 µL.

Development Over a path of 12 cm.

Drying In a current of warm air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 5 mL of *dilute sodium hydroxide solution R* add 0.1 mL of *bromophenol blue solution R1* and 5 mL of *methylene chloride R* and shake. The lower layer is colourless. Add 0.1 mL of solution S (see Tests) and shake. A blue colour develops in the lower layer.
D. To 2 mL of solution S add 1 mL of *dilute nitric acid R*. A white precipitate is formed which dissolves upon addition of 5 mL of *ethanol (96 per cent) R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 25 mL of solution S add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Add 0.3 mL of *0.01 M sodium hydroxide*. The solution is pink. Add 0.1 mL of *methyl red solution R* and 0.5 mL of *0.01 M hydrochloric acid*. The solution is orange-red.

Volatile bases and salts of volatile bases (*2.4.1, Method B*)

Maximum 50 ppm, determined on 0.20 g.

Prepare the standard using 0.1 mL of *ammonium standard solution (100 ppm NH_4) R*. Replace heavy magnesium oxide by 2.0 mL of *strong sodium hydroxide solution R*.

Loss on drying (*2.2.32*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 2.000 g in *water R* and dilute to 100.0 mL with the same solvent. Transfer 25.0 mL of the solution to a separating funnel, add 10 mL of a 4 g/L solution of *sodium hydroxide R*, 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R* and 25 mL of *methylene chloride R*. Shake vigorously, allow to separate and discard the lower layer. Shake the upper layer with 3 quantities, each of 10 mL, of *methylene chloride R* and discard the lower layers. To the upper layer add 40 mL of *hydrochloric acid R*, allow to cool and titrate with *0.05 M potassium iodate* until the deep brown colour is almost discharged. Add 4 mL of *methylene chloride R* and continue the titration, shaking vigorously, until the lower layer is no longer brown. Carry out a blank titration using a mixture of 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R*, 20 mL of *water R* and 40 mL of *hydrochloric acid R*.

1 mL of *0.05 M potassium iodate* is equivalent to 44.81 mg of $C_{27}H_{42}ClNO_2$.

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

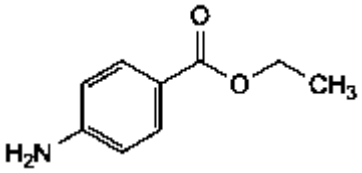
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzocaine

General Notices

(Ph. Eur. monograph 0011)



$C_9H_{11}NO_2$ 165.2 *94-09-7*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

Ethyl 4-aminobenzoate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

Second identification: B.

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison benzocaine CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in anhydrous ethanol R, evaporate to dryness and record new spectra using the residues.

B. Melting point (2.2.14).

Determination A Determine the melting point of the substance to be examined.

Result A 89 °C to 92 °C.

Determination B Mix equal parts of the substance to be examined and benzocaine CRS and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, water for chromatography R (50:50 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in 5 mL of acetonitrile R and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of 4-nitrobenzoic acid R (impurity E) in 10 mL of the solvent mixture. Dilute 1 mL of the solution to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R (3 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: dilute 1 mL of perchloric acid R to 100 mL with water for chromatography R; dilute 1 mL of this solution to 100 mL with water for chromatography R; mix 9 volumes of this solution and 1 volume of acetonitrile R1;

— *mobile phase B*: acetonitrile R1;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 15	100 → 38.5	0 → 61.5

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention With reference to benzocaine (retention time = about 10 min): impurity E = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity E and benzocaine.

Calculation of percentage contents:

— for each impurity, use the concentration of benzocaine in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the determination of primary aromatic amino-nitrogen (2.5.8), using 0.400 g dissolved in a mixture of 25 mL of *hydrochloric acid R* and 50 mL of *water R*.

1 mL of *0.1 M sodium nitrite* is equivalent to 16.52 mg of $C_9H_{11}NO_2$.

STORAGE

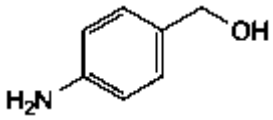
www.webofpharma.com

https://thuocngocanh.com/

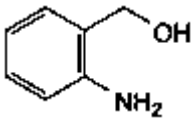
Protected from light.

IMPURITIES

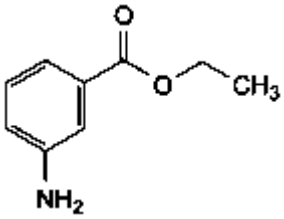
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H.



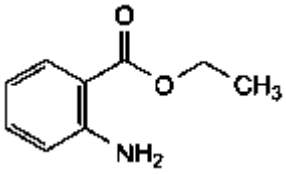
A. (4-aminophenyl)methanol,



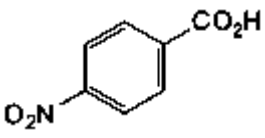
B. (2-aminophenyl)methanol,



C. ethyl 3-aminobenzoate,



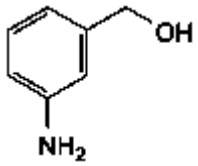
D. ethyl 2-aminobenzoate,



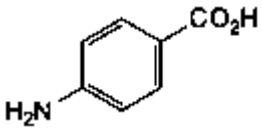
E. 4-nitrobenzoic acid,

www.webofpharma.com

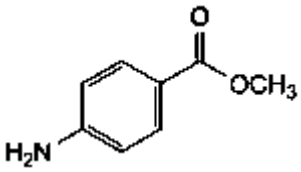
https://thuocngocanh.com/



F. (3-aminophenyl)methanol,



G. 4-aminobenzoic acid,



H. methyl 4-aminobenzoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

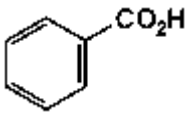
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzoic Acid

General Notices

(Ph. Eur. monograph 0066)



$C_7H_6O_2$ 122.1 *65-85-0*

Action and use

Antimicrobial preservative.

Preparations

Compound Benzoic Acid Ointment

Benzoic Acid Solution

Ph Eur

DEFINITION

Benzenecarboxylic acid.

Content

99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Slightly soluble in water, soluble in boiling water, freely soluble in ethanol (96 per cent) and in fatty oils.

IDENTIFICATION

A. Melting point (*2.2.14*): 121 °C to 124 °C.

www.webofpharma.com

https://thuocngocanh.com/

B. Solution S (see Tests) gives reaction (a) of benzoates (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *ethanol (96 per cent) R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Carbonisable substances

Dissolve 0.5 g with shaking in 5 mL of *sulfuric acid R*. After 5 min, the solution is not more intensely coloured than reference solution Y_5 (2.2.2, Method I).

Oxidisable substances

Dissolve 0.2 g in 10 mL of boiling *water R*. Cool, shake and filter. To the filtrate add 1 mL of *dilute sulfuric acid R* and 0.2 mL of *0.02 M potassium permanganate*. After 5 min, the solution is still coloured pink.

Halogenated compounds and halides

Maximum 300 ppm.

All glassware used must be chloride-free and may be prepared by soaking overnight in a 500 g/L solution of nitric acid R, rinsed with water R and stored full of water R. It is recommended that glassware be reserved for this test.

Solution (a) Dissolve 6.7 g in a mixture of 40 mL of *1 M sodium hydroxide* and 50 mL of *ethanol (96 per cent) R* and dilute to 100.0 mL with *water R*. To 10.0 mL of this solution add 7.5 mL of *dilute sodium hydroxide solution R* and 0.125 g of *nickel-aluminium alloy R* and heat on a water-bath for 10 min. Allow to cool to room temperature, filter into a 25 mL volumetric flask and wash with 3 quantities, each of 2 mL, of *ethanol (96 per cent) R*. Dilute the filtrate and washings to 25.0 mL with *water R*. This solution is used to prepare solution A.

Solution (b) In the same manner, prepare a similar solution without the substance to be examined. This solution is used to prepare solution B.

In four 25 mL volumetric flasks, place separately 10 mL of solution (a), 10 mL of solution (b), 10 mL of *chloride standard solution (8 ppm Cl) R* (used to prepare solution C) and 10 mL of *water R*. To each flask add 5 mL of *ferric ammonium sulfate solution R5*, mix and add dropwise and with swirling 2 mL of *nitric acid R* and 5 mL of *mercuric thiocyanate solution R*. Shake. Dilute the contents of each flask to 25.0 mL with *water R* and allow the solutions to stand in a water-bath at 20 °C for 15 min. Measure at 460 nm the absorbance (2.2.25) of solution A using solution B as the compensation liquid, and the absorbance of solution C using the solution obtained with 10 mL of *water R* as the compensation liquid. The absorbance of solution A is not greater than that of solution C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Dissolve 0.200 g in 20 mL of *ethanol (96 per cent) R* and titrate with *0.1 M sodium hydroxide*, using 0.1 mL of *phenol red solution R* as indicator, until the colour changes from yellow to violet-red.

1 mL of *0.1 M sodium hydroxide* is equivalent to 12.21 mg of $C_7H_6O_2$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzoic Acid Solution

General Notices

DEFINITION

Benzoic Acid	50 g
Propylene Glycol	750 mL
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

Extemporaneous preparation

The following directions apply.

Dissolve the Benzoic Acid in the Propylene Glycol and add sufficient Purified Water, in small quantities and with constant stirring, to produce 1000 mL.

Content of benzoic acid, $C_7H_6O_2$

4.75 to 5.25% w/v.

IDENTIFICATION

A. To 5 mL add 30 mL of 1M *sulfuric acid* and extract the precipitated acid with three 25-mL quantities of *petroleum spirit (boiling range, 40° to 60°)*. Wash the combined extracts with three 25-mL quantities of *water*, filter through absorbent cotton and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of benzoic acid *(RS 025)*.

B. *Melting point* of the residue obtained in test A, about 121°, Appendix V A.

TESTS

Weight per mL

1.045 to 1.055 g, Appendix V G.

ASSAY

To 10 mL add 20 mL of *ethanol (96%)* previously neutralised to *phenolphthalein solution R1* and titrate with *0.1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 12.21 mg of $C_7H_6O_2$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzoyl Peroxide and Clindamycin Gel

General Notices

Action and use

Used topically in the treatment of acne.

DEFINITION

Benzoyl Peroxide and Clindamycin Gel contains Hydrous Benzoyl Peroxide and Clindamycin Phosphate in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of anhydrous benzoyl peroxide, $C_{14}H_{10}O_4$

90.0 to 110.0% of the stated amount.

Content of clindamycin, $C_{18}H_{33}ClN_2O_5S$

92.0 to 107.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the preparation being examined containing the equivalent of 50 mg of anhydrous benzoyl peroxide with 50 mL of *dichloromethane*. Add sufficient *dichloromethane* to produce 100 mL and filter.

(2) 0.05% w/v of *benzoyl peroxide* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 2 volumes of *dichloromethane* and 50 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of the preparation being examined containing the equivalent of 20 mg of clindamycin with 5 mL of *methanol*. Add sufficient *methanol* to produce 10 mL and filter.

(2) 0.2% w/v of *clindamycin phosphate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 100° to 105° for 30 minutes, allow it to cool and spray with a 0.1% w/v solution of *potassium permanganate* and examine.

MOBILE PHASE

20 volumes of *water*, 20 volumes of *glacial acetic acid* and 60 volumes of *1-butanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the preparation being examined containing the equivalent of 20 mg of clindamycin with 5 mL of *methanol*. Add sufficient *methanol* to produce 10 mL and filter.

(2) 0.2% w/v of *clindamycin phosphate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry at 100° to 105° for 30 minutes, allow it to cool and spray with a 0.1% w/v solution of *potassium permanganate* and examine.

MOBILE PHASE

20 volumes of *water*, 20 volumes of *glacial acetic acid* and 60 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. In the test for Related substances for benzoyl peroxide, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (5).

D. In the Assay for clindamycin, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

Related substances

www.webofpharma.com

https://thuocngocanh.com/

for benzoyl peroxide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the gel containing the equivalent of 50 mg of anhydrous benzoyl peroxide with 50 mL of *acetone*, dilute to 100 mL with *acetone* and centrifuge. Dilute 1 mL of the supernatant liquid to 10 mL with *acetonitrile*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.

(3) 0.003% w/v of *benzoic acid*, 0.0003% w/v of *ethyl benzoate* and 0.0003% w/v of *benzaldehyde* in *acetonitrile*.

(4) Dilute 1 volume of solution (2) to 10 volumes with *acetonitrile*.

(5) 0.005% w/v *benzoyl peroxide* in a mixture of 1 volume of *acetone* and 9 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *polar end-capped ether-linked phenyl for chromatography* (4 µm) (Phenomenex Synergi Polar RP is suitable) fitted with a suitable stainless steel guard column packed with *octadecylsilyl silica gel for chromatography*.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.00042% v/v *orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	65	35	isocratic
5-15	65→15	35→85	linear gradient
15-18	15	85	isocratic
18-20	15→65	85→35	linear gradient
20-31	65	35	re-equilibration

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to benzoyl peroxide (retention time about 14 minutes) are: benzoic acid, about 0.3; benzaldehyde, about 0.5 and ethyl benzoate, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to benzoic acid and benzaldehyde is at least 2.0.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

Identify the peaks due to benzoic acid, benzaldehyde and ethyl benzoate using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: benzoic acid, 1.5; benzaldehyde, 1.7; and ethyl benzoate, 1.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to benzoic acid is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all *secondary peaks* excluding benzoic acid is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

for clindamycin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a solution containing *0.002% w/v* of *2-phenoxyethanol* *(internal standard)* in *0.1% v/v* *trifluoroacetic acid*.

(1) Shake a quantity of the gel containing the equivalent of 0.1 g of clindamycin with 30 mL, and then dilute to 50 mL.
(2) Dissolve 0.15 g of *clindamycin phosphate BPCRS* and 0.25 g of *benzoyl peroxide* in 10 mL of *water*, heat at 85° for 16 hours, and filter. Dilute 1 mL of the filtrate to 25 mL with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of clindamycin.

MOBILE PHASE

0.1 volume of *trifluoroacetic acid*, 17 volumes of *acetonitrile R1* and 83 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to clindamycin (retention time about 30 minutes) are: impurity A, about 0.14; impurity 1, about 0.28; impurity 2, about 0.36; impurity 3, about 0.38; impurity B, about 0.40; impurity 4, about 0.43; benzoic acid, about 0.70; impurity E, about 1.48.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (2) closely resembles the degradation chromatogram supplied with *clindamycin phosphate BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1):

Identify the peaks corresponding to impurities A, 1, 2, 3 and 4 using the chromatogram obtained with solution (2). Multiply the heights of these peaks by the corresponding correction factors: impurity A, 0.15; impurity 1, 0.26; impurity 2, 0.39; impurity 3, 0.26; impurity 4, 0.39.

Calculate the ratio of the height of the peak corresponding to clindamycin, to the height of the peak corresponding to the internal standard (*R*).

the ratio of the height of any peak corresponding to impurity 1 to the height of the internal standard is not greater than *0.06R* (6.0%);

the ratio of the height of any peak corresponding to impurity 2 to the height of the internal standard is not greater than *0.02R* (2.0%);

the ratio of the height of any peak corresponding to impurity 3 to the height of the internal standard is not greater than *0.09R* (9.0%);

the ratio of the height of any other *secondary peak* to the height of the internal standard is not greater than 0.01R (1.0%);

the sum of the ratios of the heights of all *secondary peaks* to the height of the internal standard is not greater than *0.15R* (15.0%);

Disregard any secondary peak where the ratio of the height of the peak is less than *0.01R* (1.0%).

ASSAY

For benzoyl peroxide

Mix, with the aid of ultrasound, a weighed quantity of the gel containing the equivalent of 10 mg of anhydrous benzoyl peroxide with 5 mL of *dimethylformamide* and 25 mL of *acetone*. Add 5 mL of a 50% w/v solution of *potassium iodide*. Titrate with 0.1M *sodium thiosulfate VS* using *starch solution*, added towards the end of the titration, as indicator. Carry out a blank titration using 5 mL of *dimethylformamide* and 25 mL of *acetone*. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 1.211 mg of $C_{14}H_{10}O_4$.

For clindamycin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a solution containing 0.002% w/v of *2-phenoxyethanol* *(internal standard)* in 0.1% v/v *trifluoroacetic acid*.

(1) Shake a quantity of the gel containing the equivalent of 10 mg of clindamycin with 30 mL, and then dilute to 50 mL.
(2) 0.02% w/v of clindamycin phosphate BPCRS
(3) Dissolve 0.15 g of *clindamycin phosphate BPCRS* and 0.25 g of *benzoyl peroxide* in 10 mL of *water*, heat at 85° for 16 hours, and filter. Dilute 1 volume of the filtrate to 25 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

https://thuocngocanh.com/

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the degradation chromatogram supplied with *clindamycin phosphate BPCRS*.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{33}ClN_2O_5S$ in the gel from the chromatograms obtained and from the declared content of $C_{18}H_{34}ClN_2O_8PS$ in *clindamycin phosphate BPCRS*. Each mg of $C_{18}H_{34}ClN_2O_8PS$ is equivalent to 0.8416 mg of $C_{18}H_{33}ClN_2O_5S$.

STORAGE

Benzoyl Peroxide and Clindamycin Gel should be stored at a temperature of 2° to 8°. It should not be allowed to freeze.

LABELLING

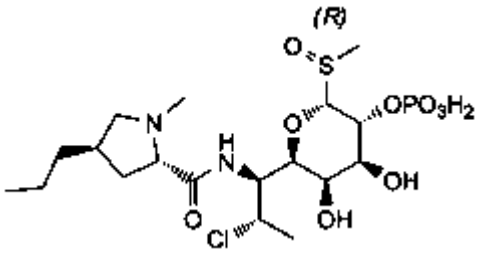
The content of Hydrous Benzoyl Peroxide is stated in terms of the equivalent amount of anhydrous benzoyl peroxide.

The content of Clindamycin Phosphate is stated in terms of the equivalent amount of clindamycin.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and E listed under Clindamycin Phosphate and the following:

1. [(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*S*,2*S*)-2-chloro-1-{[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]formamido]propyl]-4,5-dihydroxy-2-[(*R*)-methanesulfinyl]oxan-3-yl dihydrogen phosphate.

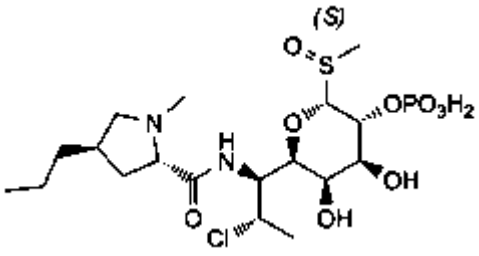


2. (2*S*,4*R*)-*N*-{(1*S*,2*S*)-2-chloro-1-[(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-methanesulfinyloxan-2-yl}propyl-1-methyl-4-propylpyrroliin-2-carboxamide.

3. [(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*S*,2*S*)-2-chloro-1-{[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl] formamido]propyl]-4,5-dihydroxy-2-[(*S*)-methanesulfinyl]oxan-3-yl dihydrogen phosphate.

www.webofpharma.com

https://thuocngocanh.com/



4. (2*S*,4*R*)-*N*-{(1*S*,2*S*)-2-chloro-1-[(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-[(ξ)-methanesulfinyl]oxan-2-yl}propyl-1-methyl-4-propylpyrroliin-2-carboxamide.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzoyl Peroxide Cream

General Notices

Action and use

Used topically in the treatment of acne.

DEFINITION

Benzoyl Peroxide Cream contains Hydrous Benzoyl Peroxide in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of anhydrous benzoyl peroxide, $C_{14}H_{10}O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

(1) Shake a quantity of the preparation being examined containing the equivalent of 50 mg of anhydrous benzoyl peroxide with 10 mL of *dichloromethane* and filter.

(2) 0.5% w/v of *benzoyl peroxide* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 2 volumes of *dichloromethane* and 50 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the test for Related substances, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to benzoyl peroxide in the chromatogram obtained with solution (4).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a mixture of 0.1 volumes of *acetic acid* and 999.9 volumes of *acetonitrile* (solvent A).

(1) Add 1 mL of solvent A to a quantity of the cream containing the equivalent of 25 mg of anhydrous benzoyl peroxide. Mix using a vortex mixer until a uniform suspension is obtained. Add three 1-mL quantities of *acetonitrile* and mix using a vortex mixer between each addition. Add a further 15 mL of *acetonitrile* and mix with the aid of ultrasound for 3 minutes. Add sufficient *acetonitrile* to produce 100 mL. Dilute 1 volume to 10 volumes with *acetonitrile*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.

(3) 0.003% w/v of *benzoic acid*, 0.0003% w/v of *ethyl benzoate* and 0.0003% w/v of *benzaldehyde* in *acetonitrile*.

(4) 0.0025% w/v of *benzoyl peroxide* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped phenyl ethyl silica gel for chromatography* (4 µm) (Phenomenex Synergi Polar RP is suitable) fitted with a suitable stainless steel guard column packed with *octadecylsilyl silica gel for chromatography*.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.00042% v/v *Orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	65	35	isocratic
5-15	65→15	35→85	linear gradient
15-18	15	85	isocratic
18-20	15→65	85→35	linear gradient
20-31	65	35	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to benzoyl peroxide (retention time, about 14.5 minutes) are: benzoic acid, about 0.3; benzaldehyde, about 0.5 and ethyl benzoate, about 0.8.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to benzoic acid and benzaldehyde is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

Identify the peaks due to benzoic acid, benzaldehyde and ethyl benzoate using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: benzoic acid, 1.50; benzaldehyde, 1.74; and ethyl benzoate, 1.72.

the area of any peak corresponding to benzoic acid is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (10%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Mix a quantity of the preparation being examined containing the equivalent of 0.25 g of anhydrous benzoyl peroxide with 50 mL of *acetone* and add sufficient *acetone* to produce 100 mL. To 10 mL add 25 mL of a 20% w/v solution of *potassium iodide*, mix, stopper the flask and allow to stand for 15 minutes protected from light. Add 25 mL of *acetone* and titrate with 0.01M *sodium thiosulfate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.01M *sodium thiosulfate VS* is equivalent to 1.211 mg of $C_{14}H_{10}O_4$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous benzoyl peroxide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzoyl Peroxide Gel

General Notices

Action and use

Used topically in the treatment of acne.

DEFINITION

Benzoyl Peroxide Gel is a solution of Hydrous Benzoyl Peroxide in a suitable water-soluble basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of anhydrous benzoyl peroxide, $C_{14}H_{10}O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

(1) Shake a quantity of the preparation being examined containing the equivalent of 50 mg of anhydrous benzoyl peroxide with 10 mL of *dichloromethane* and filter.

(2) 0.5% w/v of *benzoyl peroxide* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 2 volumes of *dichloromethane* and 50 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the test for Related substances, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to benzoyl peroxide in the chromatogram obtained with solution (4).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a mixture of 0.1 volumes of *acetic acid* and 999.9 volumes of *acetonitrile* (solvent A).

(1) Add 1 mL of solvent A to a quantity of the gel containing the equivalent of 25 mg of anhydrous benzoyl peroxide. Mix using a vortex mixer until a uniform suspension is obtained. Add three 1-mL quantities of *acetonitrile* and mix using a vortex mixer between each addition. Add a further 15 mL of *acetonitrile* and mix with the aid of ultrasound for 3 minutes. Add sufficient *acetonitrile* to produce 100 mL. Dilute 1 volume to 10 volumes with *acetonitrile*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.

(3) 0.003% w/v of *benzoic acid*, 0.0003% w/v of *ethyl benzoate* and 0.0003% w/v of *benzaldehyde* in *acetonitrile*.

(4) 0.0025% w/v of *benzoyl peroxide* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped phenyl ethyl silica gel for chromatography* (4 µm) (Phenomenex Synergi Polar RP is suitable) fitted with a suitable stainless steel guard column packed with *octadecylsilyl silica gel for chromatography*.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.00042% v/v of *orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	65	35	isocratic
5-15	65→15	35→85	linear gradient
15-18	15	85	isocratic
18-20	15→65	85→35	linear gradient
20-31	65	35	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to benzoyl peroxide (retention time about 14.5 minutes) are: benzoic acid, about 0.3; benzaldehyde, about 0.5 and ethyl benzoate, about 0.8.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to benzoic acid and benzaldehyde is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

Identify the peaks due to benzoic acid, benzaldehyde and ethyl benzoate using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: benzoic acid, 1.50; benzaldehyde, 1.74; and ethyl benzoate, 1.72.

the area of any peak corresponding to benzoic acid is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (10%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Mix a quantity of the preparation being examined containing the equivalent of 0.25 g of anhydrous benzoyl peroxide with 50 mL of *acetone* and add sufficient *acetone* to produce 100 mL. To 10 mL add 25 mL of a 20% w/v solution of *potassium iodide*, mix, stopper the flask and allow to stand for 15 minutes protected from light. Add 25 mL of *acetone* and titrate with 0.01M *sodium thiosulfate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of sodium thiosulfate required. Each ml of 0.01M *sodium thiosulfate VS* is equivalent to 1.211 mg of $C_{14}H_{10}O_4$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous benzoyl peroxide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzoyl Peroxide Lotion

General Notices

Benzoyl Peroxide Cutaneous Suspension

Action and use

Used topically in the treatment of acne.

DEFINITION

Benzoyl Peroxide Lotion is a *cutaneous suspension*. It contains Hydrous Benzoyl Peroxide in a suitable non-greasy vehicle.

The lotion complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of anhydrous benzoyl peroxide, $C_{14}H_{10}O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

(1) Shake a quantity of the preparation being examined containing the equivalent of 50 mg of anhydrous benzoyl peroxide with 10 mL of *dichloromethane* and filter.

(2) 0.5% w/v of *benzoyl peroxide* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 2 volumes of *dichloromethane* and 50 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the test for Related substances, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to benzoyl peroxide in the chromatogram obtained with solution (4).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a mixture of 0.1 volumes of *acetic acid* and 999.9 volumes of *acetonitrile* (solvent A).

(1) Add 1 mL of solvent A to a quantity of the lotion containing the equivalent of 25 mg of anhydrous benzoyl peroxide. Mix using a vortex mixer until a uniform suspension is obtained. Add three 1-mL quantities of *acetonitrile* and mix using a vortex mixer between each addition. Add a further 15 mL of *acetonitrile* and mix with the aid of ultrasound for 3 minutes. Add sufficient *acetonitrile* to produce 100 mL. Dilute 1 volume to 10 volumes with *acetonitrile*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.

(3) 0.003% w/v of *benzoic acid*, 0.0003% w/v of *ethyl benzoate* and 0.0003% w/v of *benzaldehyde* in *acetonitrile*.

(4) 0.0025% w/v of *benzoyl peroxide* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped phenylethyl silica gel for chromatography* (4 µm) (Phenomenex Synergi Polar RP is suitable) fitted with a suitable stainless steel guard column packed with *octadecylsilyl silica gel for chromatography*.

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.00042% v/v *Orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	65	35	isocratic
5-15	65→15	35→85	linear gradient
15-18	15	85	isocratic
18-20	15→65	85→35	linear gradient
20-31	65	35	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to benzoyl peroxide (retention time, about 14.5 minutes) are: benzoic acid, about 0.3; benzaldehyde, about 0.5 and ethyl benzoate, about 0.8.

www.webofpharma.com

https://thietbiuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to benzoic acid and benzaldehyde is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

Identify the peaks due to benzoic acid, benzaldehyde and ethyl benzoate using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the corresponding correction factors: benzoic acid, 1.50; benzaldehyde, 1.74; and ethyl benzoate, 1.72.

the area of any peak corresponding to benzoic acid is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (10%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Mix a quantity of the preparation being examined containing the equivalent of 0.25 g of anhydrous benzoyl peroxide with 50 mL of *acetone* and add sufficient *acetone* to produce 100 mL. To 10 mL add 25 mL of a 20% w/v solution of *potassium iodide*, mix, stopper the flask and allow to stand for 15 minutes protected from light. Add 25 mL of *acetone* and titrate with 0.01M *sodium thiosulfate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.01M *sodium thiosulfate VS* is equivalent to 1.211 mg of $C_{14}H_{10}O_4$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous benzoyl peroxide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzydamine Cream

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Benzydamine Cream contains Benzydamine Hydrochloride in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of benzydamine hydrochloride, $C_{19}H_{23}N_3O,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Heat a quantity of the cream containing 25 mg of Benzydamine Hydrochloride with 50 mL of *absolute ethanol* until the cream is completely dissolved and place in an ice-bath until a white precipitate forms. Allow to warm to 20°, dilute to 100 mL with *absolute ethanol* and filter. Dilute 10 mL of the filtrate to 100 mL with *absolute ethanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum at 308 nm.

B. In the test for 1-Benzyl-1*H*-indazol-3-ol, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

1-Benzyl-1*H*-indazol-3-ol

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Extract a quantity of the cream containing 60 mg of Benzydamine Hydrochloride with 25 mL of hot *methanol*, cool the solution in ice and filter; repeat the extraction twice, filtering each extract and evaporate the combined extracts to dryness using a rotary evaporator; dissolve the residue in 5 mL of *methanol*.

(2) 1.2% w/v of *benzydamine hydrochloride BPCRS*.

(3) 0.0024% w/v of *1-benzyl-1*H*-indazol-3-ol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Apply 40 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm* and *365 nm)*.

MOBILE PHASE

30 volumes of *triethylamine* and 80 volumes of *toluene*.

LIMITS

By each method of visualisation, any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.2%).

ASSAY

To a quantity of the cream containing 25 mg of Benzydamine Hydrochloride add 50 mL of *ethanol (96%)*, heat until the cream is completely dissolved and cool in an ice-bath until a white precipitate forms. Allow to warm to 20°, dilute to 100 mL with *ethanol (96%)* and filter. Dilute 10 mL of the filtrate to 100 mL with *ethanol (96%)* and measure the *absorbance* of the resulting solution at the maximum at about 308 nm, Appendix II B, using *ethanol (96%)* in the reference cell. Calculate the content of $C_{19}H_{23}N_3O$,HCl from the *absorbance* obtained with a solution containing 0.0025% w/v of *benzydamine hydrochloride BPCRS* in *ethanol (96%)* and using the declared content of $C_{19}H_{23}N_3O$,HCl in *benzydamine hydrochloride BPCRS*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

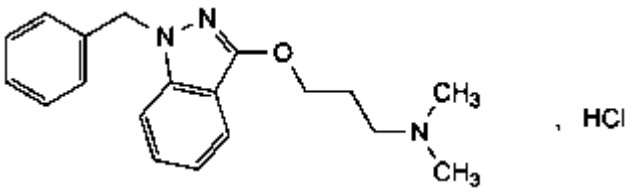
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Benzydamine Hydrochloride

General Notices

(Ph. Eur. monograph 2759)



$C_{19}H_{24}ClN_3O$ 345.9 *132-69-4*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Benzydamine Cream

Benzydamine Mouthwash

Benzydamine Oromucosal Spray

Ph Eur

DEFINITION

3-[(1-Benzyl-1*H*-indazol-3-yl)oxy]-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Very soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride, slightly soluble in acetone, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison benzydamine hydrochloride CRS.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Impurity G

Liquid chromatography (2.2.29) coupled with mass spectrometry (2.2.43).

Solvent mixture Mobile phase A, mobile phase B (8:92 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution Dissolve 5.0 mg of benzydamine impurity G CRS in methanol R and dilute to 1000.0 mL with methanol R. Dilute 1.0 mL of this solution to 1000.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 3.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R (2.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: in 1000 mL of methanol R3 mix 500 µL of formic acid R and 130 µL of heptafluorobutyric acid R;

— *mobile phase B*: in 1000 mL of water for chromatography R mix 500 µL of formic acid R and 130 µL of heptafluorobutyric acid R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	8	92
9 - 15	8 → 26	92 → 74
15 - 15.1	26 → 80	74 → 20
15.1 - 20	80	20

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 0.3 mL/min.

Detection Mass detector: the following settings have been found to be suitable for triple-quadrupole mass spectrometer and are given as examples; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criteria:

— *ionisation*: ESI-positive;

— *ion spray voltage*: 5.5 kV;

— *ion source temperature*: 350 °C;

— *declustering potential*: 67 V;

— *Q1/Q3 resolution*: unit resolution;

— *dwell time*: 500 ms;

— *acquisition starting time*: 4 min;

— *acquisition ending time*: 16 min;

— *ion transition*: 122.1 *m/z* to 46.0 *m/z*;

— *collision energy*: 30 eV.

Injection 6 µL.

Retention time Impurity G = about 7 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 5.0 per cent for the area of the peak due to impurity G determined on 6 injections using the extracted ion chromatogram showing the total ion current of the ion transition used for quantification.

Calculation of content:

— use the concentration of impurity G in the reference solution.

Limit:

— *impurity G*: maximum 5 ppm.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture methanol R, water R (50:50 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *benzydamine for system suitability CRS* (containing impurities A, B and D) in 5 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amidoalkylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 1.36 g of *potassium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, adjust to pH 3.0 with *phosphoric acid R*, add 1.16 g of *sodium octanesulfonate R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	50	50
2 - 22	50 → 35	50 → 65
22 - 29	35	65

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 320 nm.

Equilibration At least 10 min with the mobile phase at the initial composition.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *benzydamine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and D.

Relative retention With reference to benzydamine (retention time = about 12 min): impurity A = about 1.36; impurity D = about 1.43; impurity B = about 2.0.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities A and D in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 38 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

www.webofpharma.com

https://thuocngocanh.com/

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.9; impurity D = 1.4;

— for each impurity, use the concentration of benzydamine hydrochloride in reference solution (a).

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurity A*: maximum 0.2 per cent;

— *impurity D*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 34.59 mg of $C_{19}H_{24}ClN_3O$.

STORAGE

In an airtight container.

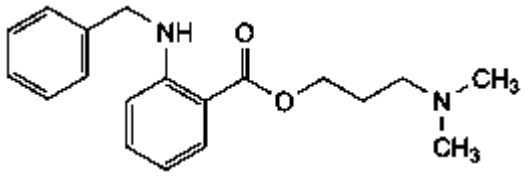
IMPURITIES

Specified impurities *A, B, D, G*.

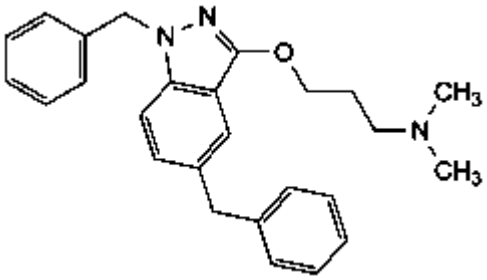
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, F*.

www.webofpharma.com

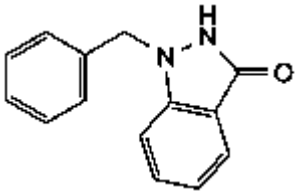
https://thuocngocanh.com/



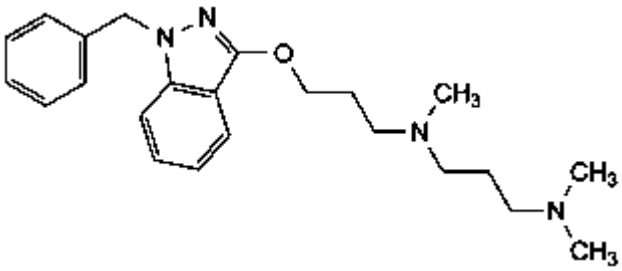
A. 3-(dimethylamino)propyl 2-(benzylamino)benzoate,



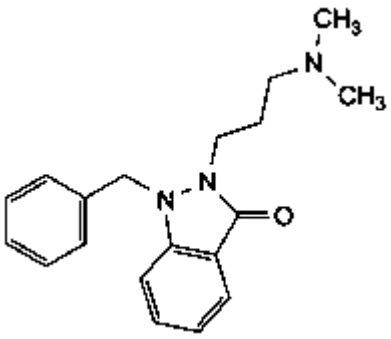
B. 3-[(1,5-dibenzyl-1*H*-indazol-3-yl)oxy]-*N*,*N*-dimethylpropan-1-amine,



C. 1-benzyl-1,2-dihydro-3*H*-indazol-3-one,



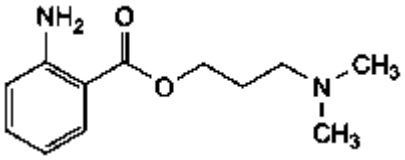
D. N^1-[3-[(1-benzyl-1*H*-indazol-3-yl)oxy]propyl]-N^1,N^3,N^3-trimethylpropane-1,3-diamine,



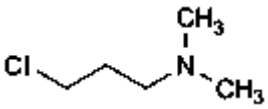
E. 1-benzyl-2-[3-(dimethylamino)propyl]-1,2-dihydro-3*H*-indazol-3-one,

www.webofpharma.com

https://thuocngocanh.com/



F. 3-(dimethylamino)propyl 2-aminobenzoate,



G. 3-chloro-*N*,*N*-dimethylpropan-1-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzydamine Mouthwash

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Benzydamine Mouthwash is a solution of Benzydamine Hydrochloride in a suitable flavoured and coloured vehicle.

The mouthwash complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of benzydamine hydrochloride, $C_{19}H_{23}N_3O,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the mouthwash, if necessary, with *absolute ethanol* to contain 0.15% w/v of Benzydamine Hydrochloride.

(2) 0.15% w/v of *benzydamine hydrochloride BPCRS* in *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254} precoated plate* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

30 volumes of *triethylamine* and 80 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

www.webofpharma.com

https://thuocngocanh.com/

5.0 to 7.0, Appendix V L.

1-Benzyl-1*H*-indazol-3-ol

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the mouthwash containing 15 mg of Benzydamine Hydrochloride with seven 90-mL quantities of *chloroform*. Filter each extract through phase separating paper, evaporate the combined extracts to dryness and dissolve the residue in 10 mL of *methanol*.
(2) 0.0015% w/v of *1-benzyl-1*H*-indazol-3-ol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel* F_{254} *plate*.
(b) Use the mobile phase as described below.
(c) Apply 20 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

10 volumes of *glacial acetic acid*, 20 volumes of *chloroform* and 70 volumes of *cyclohexane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. Prepare a 0.075% w/v solution of *1-benzyl-3-(3-diethylamino-propoxy)-1*H*-indazole BPCRS* (internal standard) in *water* (solution A).

(1) Add 10 mL of solution A, 5 mL of *water*, 5 mL of 1M *sodium hydroxide* and 20 mL of *chloroform* to a quantity of the mouthwash containing 7.5 mg of Benzydamine Hydrochloride, diluted, if necessary to 5 mL with *water*, shake for 5 minutes, centrifuge and use the chloroform layer.
(2) Prepare solution (2) in the same manner as solution (1) except using 5 mL of a solution containing 0.15% w/v of *benzydamine hydrochloride BPCRS* in *water* in place of a quantity of the mouthwash containing 7.5 mg of Benzydamine Hydrochloride, diluted, if necessary, to 5 mL with *water*.

CHROMATOGRAPHIC CONDITIONS

a) Use a glass column (2 m × 2 mm) packed with *acid-washed, diatomaceous support* (80 to 100 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable).
(b) Use *nitrogen for chromatography* as the carrier gas at 30 mL per minute.
(c) Use isothermal conditions maintained at 260°.
(d) Use an inlet temperature of 300°.
(e) Use a flame ionisation detector at 300°.
(f) Inject 1 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{23}N_3O$,HCl from the chromatograms obtained using the declared content of $C_{19}H_{23}N_3O$,HCl in *benzydamine hydrochloride BPCRS*.

LABELLING

The label states, where appropriate, that the preparation is also suitable for use as a gargle.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzydamine Oromucosal Spray

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Benzydamine Oromucosal Spray is a solution of Benzydamine Hydrochloride in a suitable flavoured vehicle in a suitable metered-dose container.

The oromucosal spray complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of benzydamine hydrochloride, $C_{19}H_{23}N_3O,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the oromucosal spray, if necessary, with *absolute ethanol* to contain 0.15% w/v of Benzydamine Hydrochloride.

(2) 0.15% w/v of *benzydamine hydrochloride BPCRS* in *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254} precoated plate* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

30 volumes of *triethylamine* and 80 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity or alkalinity

5.0 to 7.0, Appendix V L.

Uniformity of weight

Weigh one unit. Fire one shot and reweigh the unit. Repeat four times, then repeat the entire process with 3 more units (20 shots). Determine the average weight delivered per shot. Not more than two of the individual weights deviate from the average weight by more than 10% and none deviates by more than 20%.

1-Benzyl-1*H*-indazol-3-ol

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the oromucosal spray containing 15 mg of Benzydamine Hydrochloride with seven 90-mL quantities of *chloroform*. Filter each extract through phase separating paper, evaporate the combined extracts to dryness and dissolve the residue in 10 mL of *methanol*.

(2) 0.0015% w/v of *1-benzyl-1*H*-indazol-3-ol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254} plate*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

10 volumes of *glacial acetic acid*, 20 volumes of *chloroform* and 70 volumes of *cyclohexane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B using the following solutions. Prepare a 0.075% w/v solution of *1-benzyl-3-(3-diethylamino-propoxy)-1*H*-indazole BPCRS* (internal standard) in *water* (solution A).

(1) Add 10 mL of solution A, 5 mL of *water*, 5 mL of 1M *sodium hydroxide* and 20 mL of *chloroform* to a quantity of the oromucosal spray containing 7.5 mg of Benzydamine Hydrochloride, diluted, if necessary to 5 mL with *water*, shake for 5 minutes, centrifuge and use the chloroform layer.

(2) Prepare solution (2) in the same manner as solution (1) but using 5 mL of solution containing 0.15% w/v of *benzydamine hydrochloride BPCRS* in *water* in place of a quantity of the oromucosal spray containing 7.5 mg of Benzydamine Hydrochloride, diluted, if necessary, to 5 mL with *water*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a glass column (2 m × 2 mm) packed with *acid-washed, diatomaceous support* (80 to 100 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable).

(b) Use *nitrogen for chromatography* as the carrier gas at 30 mL per minute.

(c) Use isothermal conditions maintained at 260°.

(d) Use an inlet temperature of 300°.

(e) Use a flame ionisation detector at 300°.

(f) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{23}N_3O$,HCl from the chromatograms obtained using the declared content of $C_{19}H_{23}N_3O$,HCl in *benzydamine hydrochloride BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

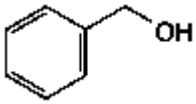
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzyl Alcohol[1]

General Notices

(Ph. Eur. monograph 0256)



C_7H_8O 108.1 *100-51-6*

Action and use

Local anaesthetic; disinfectant.

Ph Eur

DEFINITION

Phenylmethanol.

Content

98.0 per cent to 100.5 per cent.

♦ CHARACTERS

Appearance

Clear, colourless, oily liquid.

Solubility

Soluble in water, miscible with ethanol (96 per cent) and with fatty and essential oils.

Relative density

1.043 to 1.049.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *benzyl alcohol CRS*.♦

www.webofpharma.com

https://thuocngocanh.com/

TESTS

♦ Appearance of solution

Shake 2.0 mL with 60 mL of *water R*. It dissolves completely. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).♦

Acidity

To 10 mL add 10 mL of *ethanol (96 per cent) R* and 1 mL of *phenolphthalein solution R*. Not more than 1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Refractive index (*2.2.6*)

1.538 to 1.541.

Peroxide value (*2.5.5, Method A*)

Maximum 5.

Related substances

Gas chromatography (*2.2.28*).

Test solution The substance to be examined.

Standard solution (a) Dissolve 0.100 g of *ethylbenzene R* in the test solution and dilute to 10.0 mL with the same solution. Dilute 2.0 mL of this solution to 20.0 mL with the test solution.

Standard solution (b) Dissolve 2.000 g of *dicyclohexyl R* in the test solution and dilute to 10.0 mL with the same solution. Dilute 2.0 mL of this solution to 20.0 mL with the test solution.

Reference solution (a) Dissolve 0.750 g of *benzaldehyde R* and 0.500 g of *cyclohexylmethanol R* in the test solution and dilute to 25.0 mL with the test solution. Add 1.0 mL of this solution to a mixture of 2.0 mL of standard solution (a) and 3.0 mL of standard solution (b) and dilute to 20.0 mL with the test solution.

Reference solution (b) Dissolve 0.250 g of *benzaldehyde R* and 0.500 g of *cyclohexylmethanol R* in the test solution and dilute to 25.0 mL with the test solution. Add 1.0 mL of this solution to a mixture of 2.0 mL of standard solution (a) and 2.0 mL of standard solution (b) and dilute to 20.0 mL with the test solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

www.webofpharma.com

https://thuocngocanh.com/

Linear velocity 25 cm/s at 50 °C.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 34	50 → 220
	34 - 69	220
Injection port		200
Detector		310

Detection Flame ionisation.

Benzyl alcohol not intended for parenteral administration

Injection Without air-plug, 0.1 µL of the test solution and reference solution (a).

Relative retention With reference to benzyl alcohol (retention time = about 26 min): ethylbenzene = about 0.28; dicyclohexyl = about 0.59; impurity A = about 0.68; impurity B = about 0.71.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurities A and B.

If any peaks in the chromatogram obtained with the test solution have the same retention time as the peaks due to ethyl benzene or dicyclohexyl, subtract the areas of any such peaks from the peak areas at these retention times in the chromatograms obtained with reference solutions (a) or (b) (corrected peak areas of ethyl benzene and dicyclohexyl). Any such peaks in the chromatogram obtained with the test solution are to be included in the assessments for the sum of other peaks.

Limits:

— *impurity A*: not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (a) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.15 per cent);

— *impurity B*: not more than the difference between the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) and the area of the peak due to impurity B in the chromatogram obtained with the test solution (0.10 per cent);

— *sum of other peaks with a relative retention less than that of benzyl alcohol*: not more than 4 times the area of the peak due to ethylbenzene in the chromatogram obtained with reference solution (a) corrected if necessary as described above (0.04 per cent);

— *sum of peaks with a relative retention greater than that of benzyl alcohol*: not more than the area of the peak due to dicyclohexyl in the chromatogram obtained with reference solution (a) corrected if necessary as described above (0.3 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.01 times the area of the peak due to ethylbenzene in the chromatogram obtained with reference solution (a) corrected if necessary as described above (0.0001 per cent).

Benzyl alcohol intended for parenteral administration

Injection Without air-plug, 0.1 µL of the test solution and reference solution (b).

Relative retention With reference to benzyl alcohol (retention time = about 26 min): ethylbenzene = about 0.28; dicyclohexyl = about 0.59; impurity A = about 0.68; impurity B = about 0.71.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurities A and B.

If any peaks in the chromatogram obtained with the test solution have the same retention times as the peaks due to ethyl benzene or dicyclohexyl, subtract the areas of any such peaks from the peak areas at these retention times in the chromatograms obtained with reference solutions (a) or (b) (corrected peak areas of ethyl benzene and dicyclohexyl). Any such peaks in the chromatogram obtained with the test solution are to be included in the assessments for the sum of other peaks.

Limits:

— *impurity A*: not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.05 per cent);

— *impurity B*: not more than the difference between the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity B in the chromatogram obtained with the test solution (0.10 per cent);

— *sum of other peaks with a relative retention less than that of benzyl alcohol*: not more than twice the area of the peak due to ethylbenzene in the chromatogram obtained with reference solution (b) corrected if necessary as described above (0.02 per cent);

— *sum of peaks with a relative retention greater than that of benzyl alcohol*: not more than the area of the peak due to dicyclohexyl in the chromatogram obtained with reference solution (b) corrected if necessary as described above (0.2 per cent);

— *disregard limit*: 0.01 times the area of the peak due to ethylbenzene in the chromatogram obtained with reference solution (b) corrected if necessary as described above (0.0001 per cent).

Residue on evaporation

Maximum 0.05 per cent.

After ensuring that the substance to be examined complies with the test for peroxide value, evaporate 10.0 g to dryness in a tared quartz or porcelain crucible or platinum dish on a hot plate at a temperature not exceeding 200 °C. Ensure that the substance to be examined does not boil during evaporation. Dry the residue on the hot plate for 1 h and allow to cool in a desiccator. The residue weighs a maximum of 5 mg.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

To 0.900 g (*m* g) add 15.0 mL of a freshly prepared mixture of 1 volume of *acetic anhydride R* and 7 volumes of *anhydrous pyridine R* and heat under a reflux condenser on awater-bath for 30 min. Cool and add 25 mL of *water R*. Using 0.25 mL of *phenolphthalein solution R* as indicator, titrate with *1 M sodium hydroxide* (n_1 mL). Carry out a blank titration (n_2 mL).

Calculate the percentage content of C_7H_8O using the following expression:

$$\frac{10.81\left(n_2 - n_1\right)}{m}$$

♦ STORAGE

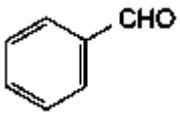
In an airtight container, under nitrogen, protected from light and at a temperature between 2 °C and 8 °C.

LABELLING

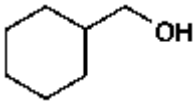
The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.♦

IMPURITIES

Specified impurities *A, B.*



A. benzaldehyde,



B. cyclohexylmethanol.

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

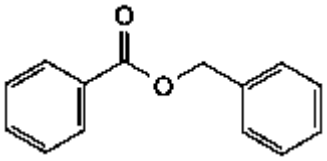
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzyl Benzoate

General Notices

(Ph. Eur. monograph 0705)



$C_{14}H_{12}O_2$ 212.2 *120-51-4*

Action and use

Used topically in the treatment of scabies.

Preparation

Benzyl Benzoate Application

Ph Eur

DEFINITION

Phenylmethyl benzoate.

Content

99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

Colourless or almost colourless crystals or colourless or almost colourless, oily liquid.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent), with methylene chloride and with fatty and essential oils.

bp

About 320 °C.

IDENTIFICATION

https://thuocngocanh.com/

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of benzyl benzoate*.

B. To 2 g add 25 mL of *alcoholic potassium hydroxide solution R* and boil under a reflux condenser for 2 h. Remove the ethanol on a water-bath, add 50 mL of *water R* and distill. Collect about 25 mL of distillate and use it for identification test C. Acidify the liquid remaining in the distillation flask with *dilute hydrochloric acid R*. A white precipitate is formed that, when washed with *water R* and dried *in vacuo* melts (2.2.14) at 121 °C to 124 °C.

C. To the distillate obtained in identification test B add 2.5 g of *potassium permanganate R* and 5 mL of *dilute sodium hydroxide solution R*. Boil under a reflux condenser for 15 min, cool and filter. Acidify the filtrate with *dilute hydrochloric acid R*. A white precipitate is formed that, when washed with *water R* and dried *in vacuo*, melts (2.2.14) at 121 °C to 124 °C.

TESTS

Acidity

Dissolve 2.0 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent. Titrate with *0.1 M sodium hydroxide* using *phenolphthalein solution R* as indicator. Not more than 0.2 mL is required to change the colour of the indicator to pink.

Relative density (2.2.5)

1.118 to 1.122.

Refractive index (2.2.6)

1.568 to 1.570.

Freezing point (2.2.18)

Minimum 17.0 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

To 2.000 g add 50.0 mL of *0.5 M alcoholic potassium hydroxide* and boil gently under a reflux condenser for 1 h. Titrate the hot solution with *0.5 M hydrochloric acid* using 1 mL of *phenolphthalein solution R* as indicator. Carry out a blank determination.

1 mL of *0.5 M alcoholic potassium hydroxide* is equivalent to 106.1 mg of $C_{14}H_{12}O_2$.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

In an airtight, well-filled container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzyl Benzoate Application

General Notices

Benzyl Benzoate Cutaneous Emulsion

DEFINITION

Benzyl Benzoate Application is a *cutaneous emulsion*. It contains 25% w/v of Benzyl Benzoate in a suitable oil-in-water emulsified basis.

Extemporaneous preparation

The following formula and directions apply.

Benzyl Benzoate	250 g
Emulsifying Wax	20 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

Melt the Emulsifying Wax, add the Benzyl Benzoate and mix. Pour the mixture into sufficient warm Purified Water to produce 1000 mL and stir thoroughly until cold.

The application complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of benzyl benzoate, $C_{14}H_{12}O_2$

23.1 to 26.9% w/v.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve 1 g of the application in sufficient of the mobile phase to produce 100 mL and dilute 1 volume of the resulting solution to 50 volumes with the mobile phase.

(2) 0.0050% w/v of *benzyl benzoate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *water* and 70 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the application, Appendix V G, and calculate the content of $C_{14}H_{12}O_2$, weight in volume, using the declared content of $C_{14}H_{12}O_2$ in *benzyl benzoate BPCRS*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

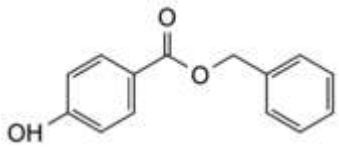
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzyl Hydroxybenzoate

General Notices

Benzylparaben



$C_{14}H_{12}O_3$ 228.3 *94-18-8*

Action and use

Antimicrobial preservative.

DEFINITION

Benzyl Hydroxybenzoate is benzyl 4-hydroxybenzoate. It contains not less than 99.0% and not more than 101.0% of $C_{14}H_{12}O_3$.

CHARACTERISTICS

A white to creamy white, crystalline powder.

Practically insoluble in *water*; freely soluble in *ethanol (96%)* and in *ether*. It dissolves in solutions of alkali hydroxides.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of benzyl hydroxybenzoate *(RS 028)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.001% w/v solution in *ethanol (96%)* exhibits a maximum only at 260 nm. The *absorbance* at the maximum at 260 nm is about 0.76.

C. Dissolve 0.1 g in 2 mL of *ethanol (96%)*, boil and add 0.5 mL of *nitric acid solution of mercury*. A precipitate is produced slowly and the supernatant liquid becomes red.

D. *Melting point*, about 112°, Appendix V A.

TESTS

Acidity

Dissolve 0.2 g in 10 mL of *ethanol (50%)* previously neutralised to *methyl red solution* and titrate with *0.1M sodium hydroxide VS* using *methyl red solution* as indicator. Not more than 0.1 mL of *0.1M sodium hydroxide VS* is required to change the colour of the solution.

Related substances

www.webofpharma.com

https://thietbiuocngocanh.com/

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a plate precoated with silica gel F_{254}, the surface of which has been modified with chemically-bonded octadecylsilyl groups (Whatman KC18F plates are suitable) and a mixture of 70 volumes of *methanol*, 30 volumes of *water* and 1 volume of *glacial acetic acid* as the mobile phase. Apply separately to the plate 2 µL of each of two solutions of the substance being examined in *acetone* containing (1) 1.0% w/v and (2) 0.010% w/v. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Gently boil 0.12 g under a reflux condenser with 20 mL of 2M *sodium hydroxide* for 30 minutes. Cool and extract with three 20-mL quantities of *1,2-dichloroethane*. Wash the combined extracts with 20 mL of 0.1M *sodium hydroxide* and add the washings to the main aqueous phase, discarding the organic layer. To the aqueous solution add 25 mL of *0.0333M potassium bromate VS*, 5 mL of a 12.5% w/v solution of *potassium bromide* and 10 mL of *hydrochloric acid* and immediately stopper the flask. Shake for 15 minutes and allow to stand for 15 minutes. Add 25 mL of *dilute potassium iodide solution* and shake vigorously. Titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of potassium bromate required. The volume of *0.0333M potassium bromate VS* used is equivalent to half of the volume of 0.1M *sodium thiosulfate VS* required for the titration. Each mL of *0.0333M potassium bromate VS* is equivalent to 7.608 mg of $C_{14}H_{12}O_3$.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

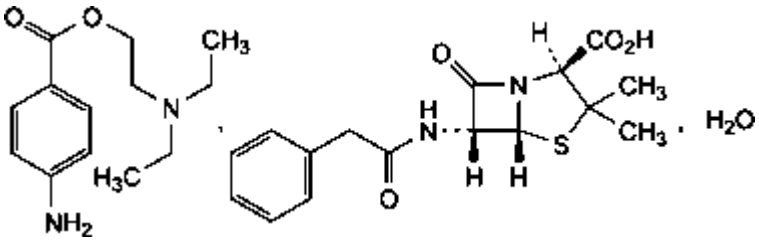
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzylpenicillin (Procaine) Monohydrate

General Notices

(Ph. Eur. monograph 0115)



$C_{29}H_{38}N_4O_6S,H_2O$ 588.7 *6130-64-9*

Action and use

Penicillin antibacterial.

Preparation

Procaine Benzylpenicillin Injection

Ph Eur

DEFINITION

2-(Diethylamino)ethyl 4-aminobenzoate (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid monohydrate.

Salt obtained from *Benzylpenicillin sodium (0114)* or *Benzylpenicillin potassium (0113)* produced by the growth of certain strains of *Penicillium notatum* or related micro-organisms.

Content

— *procaine benzylpenicillin*: 96.0 per cent to 102.0 per cent (anhydrous substance) without correction for dispersing or suspending agents;

— *procaine* ($C_{13}H_{20}N_2O_2$; M_r 236.3): 39.0 per cent to 42.0 per cent (anhydrous substance).

Dispersing or suspending agents (for example, lecithin and polysorbate 80) may be added.

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *procaine benzylpenicillin CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *acetone R*.

Reference solution Dissolve 25 mg of *procaine benzylpenicillin CRS* in 5 mL of *acetone R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* previously adjusted to pH 7.0 with *ammonia R*.

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution:

— the chromatogram shows 2 clearly separated spots.

Results The 2 principal spots in the chromatogram obtained with the test solution are similar in position, colour and size to the 2 principal spots in the chromatogram obtained with the reference solution.

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube on a water-bath for 1 min; a reddish-brown colour develops.

D. Dissolve 0.1 g in 2 mL of *dilute hydrochloric acid R*. The solution, which may be turbid, gives the reaction of primary aromatic amines (2.3.1).

TESTS

www.webofpharma.com

https://thuvienthuocngocanh.com/

pH (*2.2.3*)

5.0 to 7.5.

Dissolve 50 mg in *carbon dioxide-free water R* and dilute to 15 mL with the same solvent. Shake until dissolution is complete.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the test solutions immediately before use.*

Solvent mixture *methanol R*, *water R* (50:50 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in 25 mL of *methanol R* and dilute to 50.0 mL with *water R*.

Test solution (b) Dissolve 0.100 g of the substance to be examined in 10 mL of *methanol R* and dilute to 20.0 mL with *water R*.

Reference solution (a) Dissolve 50.0 mg of *procaine benzylpenicillin CRS* in 25 mL of *methanol R* and dilute to 50.0 mL with *water R*.

Reference solution (b) Dissolve 12.0 mg of *4-aminobenzoic acid R* (impurity A) in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*.

Reference solution (c) Dissolve 10 mg of *procaine benzylpenicillin for peak identification A CRS* (containing impurities B, C, D, E, G, H, I and J) in 1 mL of *methanol R* and add 1 mL of *water R*.

Reference solution (d) Dissolve the contents of a vial of *procaine benzylpenicillin impurity F CRS* in 1 mL of reference solution (c).

Reference solution (e) Dilute 1.0 mL of reference solution (a) to 20.0 mL with the solvent mixture.

Reference solution (f) Dilute 1.0 mL of reference solution (e) to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 10 volumes of a 68 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.4 with a 500 g/L solution of *phosphoric acid R*, 30 volumes of *methanol R1* and 60 volumes of *water for chromatography R*;

— *mobile phase B*: mix 10 volumes of a 68 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.4 with a 500 g/L solution of *phosphoric acid R*, 35 volumes of *water for chromatography R* and 55 volumes of *methanol R1*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	70	30
7 - 17	70 → 0	30 → 100
17 - 22	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL of test solution (b) and reference solutions (b), (d), (e) and (f).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram supplied with *procaine benzylpenicillin for peak identification A CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B, C, D, E, F, G, H, I and J.

Relative retention With reference to benzylpenicillin (retention time = about 7 min): procaine = about 0.19; impurity A = about 0.22; impurity D = about 0.33; impurity F = about 0.35; impurity B = about 0.48 and 0.55; impurity E = about 0.62; impurity C = about 0.81 and 0.83; impurity I = about 0.93; impurity G = about 1.47; impurity H = about 1.90; impurity J = about 2.37.

System suitability:

— *resolution*: minimum 1.0 between the peaks due to the epimers of impurity C and minimum 1.2 between the peaks due to impurities D and F in the chromatogram obtained with reference solution (d);

— *signal-to-noise ratio*: minimum 10 for the peak due to benzylpenicillin in the chromatogram obtained with reference solution (f).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 0.4;

— for impurity A, use the concentration of impurity A in reference solution (b);

— for impurities other than A, use the concentration of procaine benzylpenicillin monohydrate in reference solution (e) taking into account the area of the peak due to benzylpenicillin in the chromatogram obtained with reference solution (e).

Limits:

— *impurities F, G, H, I, J*: for each impurity, maximum 0.5 per cent;

— *impurities B (sum of isomers), C (sum of epimers)*: for each impurity, maximum 0.4 per cent;

— *impurities E, D*: for each impurity, maximum 0.2 per cent;

— *impurity A*: maximum 0.024 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *any other impurity*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to procaine.

Water (*2.5.12*)

2.8 per cent to 4.2 per cent, determined on 0.300 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (30:70 *V/V*).

Injection 10 µL of test solution (a) and reference solution (a).

Run time 3 times the retention time of benzylpenicillin.

Calculate the percentage content of procaine ($C_{13}H_{20}N_2O_2$) taking into account the area of the peak due to procaine and the assigned content of procaine ($C_{13}H_{20}N_2O_2$) in *procaine benzylpenicillin CRS*.

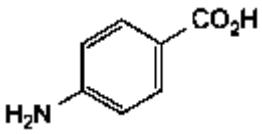
Calculate the percentage content of procaine benzylpenicillin ($C_{29}H_{38}N_4O_6S$) taking into account the area of the peak due to benzylpenicillin and the assigned content of procaine benzylpenicillin ($C_{29}H_{38}N_4O_6S$) in *procaine benzylpenicillin CRS*.

STORAGE

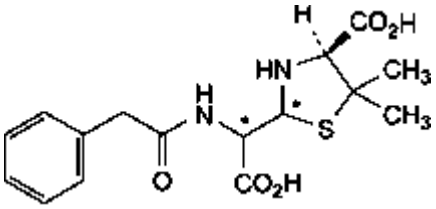
In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H, I, J.*



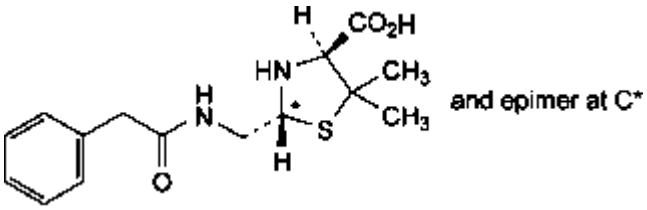
A. 4-aminobenzoic acid,



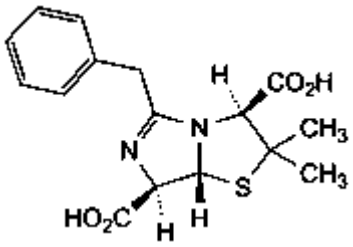
www.webofpharma.com

https://thuocngocanh.com/

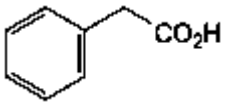
B. (2Ξ,4*S*)-2-[(Ξ)-carboxy(2-phenylacetamido)methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of benzylpenicillin),



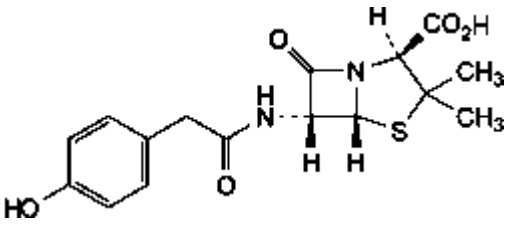
C. (2*RS*,4*S*)-5,5-dimethyl-2-[(2-phenylacetamido)methyl]-1,3-thiazolidine-4-carboxylic acid (penilloic acids of benzylpenicillin),



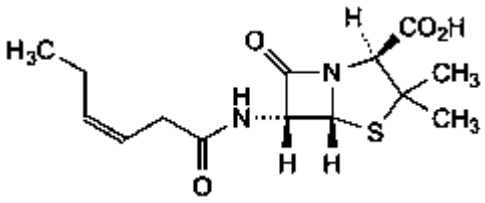
D. (3*S*,7*R*,7a*R*)-5-benzyl-2,2-dimethyl-2,3,7,7a-tetrahydroimidazo[5,1-*b*][1,3]thiazole-3,7-dicarboxylic acid (penillic acid of benzylpenicillin),



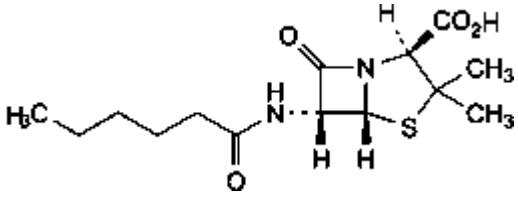
E. phenylacetic acid,



F. (2*S*,5*R*,6*R*)-6-[2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



G. (2*S*,5*R*,6*R*)-6-[(3*Z*)-hex-3-enamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (iso-penicillin F),



www.webofpharma.com

https://thuocngocanh.com/

H. (2*S*,5*R*,6*R*)-6-hexanamido-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (dihydropenicillin F),

I. unknown structure,

J. unknown structure.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzylpenicillin Eye Drops

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Penicillin antibacterial.

DEFINITION

Benzylpenicillin Eye Drops are a sterile solution of Benzylpenicillin Sodium in a suitable vehicle.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of penicillins, calculated as $C_{16}H_{18}N_2O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Dilute the eye drops, if necessary, to produce a solution containing the equivalent of 0.15% w/v of benzylpenicillin.

(2) 0.15% w/v of *benzylpenicillin sodium EPCRS*.

(3) 0.15% w/v of *benzylpenicillin sodium EPCRS* and 0.15% w/v of *phenoxymethylpenicillin potassium BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel silanised plate* (Merck silanised silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose to iodine vapour until spots appear and examine in daylight.

MOBILE PHASE

30 volumes of *acetone* and 70 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 5.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*, prepared immediately before use.

For eye drops containing the equivalent of 0.15% w/v of benzylpenicillin

(1) Use the preparation being examined.

For solutions (2) to (4), use the solutions described below.

For eye drops containing more than the equivalent of 0.15% w/v of benzylpenicillin

(1) Dilute a quantity of the eye drops, if necessary, to produce a solution containing the equivalent of 0.3% w/v of benzylpenicillin.

(2) 0.5% w/v of *benzylpenicillin for system suitability EPCRS* in a mixture of 35 volumes of *methanol R1* and 65 volumes of *water*.

(3) Dilute 1 volume of solution (1) to 100 volumes.

(4) Dilute 1 volume of solution (3) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Kromasil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of a 6.8% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 3.4 with a 50% w/v solution of *orthophosphoric acid*, 30 volumes of *methanol R1* and 60 volumes of *water*.

Mobile phase B 10 volumes of a 6.8% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 3.4 with a 50% w/v solution of *orthophosphoric acid*, 35 volumes of *water* and 55 volumes of *methanol R1*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-7	70	30	isocratic
7-17	70→0	30→100	linear gradient
17-22	0	100	isocratic

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to benzylpenicillin (retention time, about 7 minutes) are: impurity A, about 0.22; impurity D, about 0.33; impurity C; about 0.35; impurity E, about 0.48 and 0.55; impurity B, about 0.62; impurity F, about 0.81 and 0.83; impurity G, about 1.47; impurity H, about 1.90.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to the epimers of impurity F is at least 1.2 and the *resolution* between the peaks due to impurities C and D is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, D, E and F using the chromatogram obtained with solution (2) and multiply the areas of these peaks by the corresponding correction factors: impurity A, 1.3; impurity D, 0.6; impurity E, 2.0; impurity F, 1.7.

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks corresponding to impurity E is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (2.0% for the sum of the isomers);

the sum of the areas of any peaks corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1.0% for the sum of the epimers);

the area of any peak corresponding to impurity B is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*, prepared immediately before use.

(1) Dilute the eye drops to produce a solution containing the equivalent of 0.1% w/v of benzylpenicillin.

(2) 0.1% w/v of *benzylpenicillin sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used, but using the following mobile phase.

MOBILE PHASE

30 volumes of mobile phase B and 70 volumes of mobile phase A as described under Related substances.

DETERMINATION OF CONTENT

Calculate the content of penicillins, as $C_{16}H_{18}N_2O_4S$, in the eye drops using the declared content of $C_{16}H_{17}N_2NaO_4S$ in *benzylpenicillin sodium EPCRS*. Each mg of $C_{16}H_{17}N_2NaO_4S$ is equivalent to 0.9383 mg of $C_{16}H_{18}N_2O_4S$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of benzylpenicillin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Benzylpenicillin Sodium.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzylpenicillin for Injection

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Benzylpenicillin for Injection is a sterile material consisting of Benzylpenicillin Potassium or Benzylpenicillin Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of penicillins, calculated as $C_{16}H_{18}N_2O_4S$

95.0 to 105.0% of the content of benzylpenicillin stated on the label.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the spectrum of *benzylpenicillin potassium EPCRS* or *benzylpenicillin sodium EPCRS* as appropriate.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 10.0% w/v of benzylpenicillin, 5.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*, prepared immediately before use.

(1) Dissolve a quantity of the contents of a sealed container to produce a solution containing the equivalent of 0.4% w/v of benzylpenicillin.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dissolve 5 mg of *benzylpenicillin for system suitability EPCRS* in 0.35 mL of *methanol R1* and add 0.65 mL of *water*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuvienthuocngocanh.com/

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC-Pack Pro is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of a 6.8% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.4 with a 50% w/v solution of *orthophosphoric acid*, 30 volumes of *methanol R1* and 60 volumes of *water*.

Mobile phase B 10 volumes of a 6.8% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.4 with a 50% w/v solution of *orthophosphoric acid*, 35 volumes of *water* and 55 volumes of *methanol R1*.

Time (min)	Mobile Phase A (% V/V)	Mobile Phase B (% V/V)	Comment
0 - 7	70	30	isocratic
7 - 17	70 → 0	30 → 100	linear gradient
17 - 22	0	100	isocratic

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to benzylpenicillin (retention time about 7 minutes) are: impurity A, about 0.2; impurity D, about 0.3; impurity C, about 0.4; impurity E, about 0.48 and 0.55; impurity B, about 0.6; impurity F, about 0.81 and 0.83; impurity G, about 1.5 and impurity H, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to the epimers of impurity F is at least 1.2; and the resolution between the peaks due to impurities D and C is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

identify any peaks corresponding to impurities A to H using the chromatogram supplied with *benzylpenicillin for system suitability EPCRS* and the chromatogram obtained with solution (3). Multiply the area of any peaks corresponding to impurity A, impurity D, impurity E and impurity F by the following correction factors respectively: 1.3, 0.6, 2.0 and 1.7.

the sum of the areas of any peaks corresponding to the isomers of impurity E is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the sum of the areas of any peaks corresponding to the epimers of impurity F is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity B is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than 0.75 times the area of the principal peak in the chromatogram obtained with solution (4) (0.15%).

Loss on drying

When dried to constant weight at 105°, lose not more than 1.0% of their weight. Use 1 g.

Bacterial endotoxins

Carry out the test for *bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of benzylpenicillin per mL (solution A). The endotoxin limit of solution A is 1.6 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water* prepared immediately before use.

(1) Dissolve a quantity of the mixed contents of the 10 containers to produce a solution containing the equivalent of 0.1% w/v of benzylpenicillin.
(2) 0.11% w/v of *benzylpenicillin sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC-Pack Pro is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mix 10 volumes of a 6.8% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 3.5 with a 50% w/v solution of *dilute orthophosphoric acid*, 36 volumes of *methanol* and 54 volumes of *water*.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of penicillins, as $C_{16}H_{18}N_2O_4S$, in a container of average content weight using the declared content of $C_{16}H_{17}N_2NaO_4S$ in *benzylpenicillin sodium EPCRS*. Each mg of $C_{16}H_{17}N_2NaO_4S$ is equivalent to 0.9383 mg of $C_{16}H_{18}N_2O_4S$.

STORAGE

The sealed container should be stored at a temperature not exceeding 30°.

LABELLING

The label of the sealed container states (1) whether the contents are Benzylpenicillin Potassium or Benzylpenicillin Sodium; (2) the quantity of Benzylpenicillin Potassium or Benzylpenicillin Sodium contained in it in terms of the equivalent amount of benzylpenicillin.

IMPURITIES

The impurities limites by the requirements of this monograph include those listed under Benzylpenicillin Potassium and Benzylpenicillin Sodium.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzylpenicillin Infusion

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Penicillin antibacterial.

DEFINITION

Benzylpenicillin Infusion is a sterile solution containing Benzylpenicillin Sodium and a suitable buffer. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the infusion also complies with the requirements stated under Unlicensed Medicines.

Content of benzylpenicillin, $C_{16}H_{18}N_2O_4S$

90.0 to 105.0% of the stated amount.

CHARACTERS

A clear, colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Dilute a volume of the infusion to produce a solution containing the equivalent of 0.6% w/v of benzylpenicillin.

(2) 0.64% w/v of *benzylpenicillin sodium EPCRS*.

(3) 0.5% w/v of each of *benzylpenicillin sodium EPCRS* and *phenoxymethylpenicillin EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel silanised plate* (Merck silanised silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose to iodine vapour until the spots appear and examine in daylight.

MOBILE PHASE

30 volumes of *acetone* and 70 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*, prepared immediately before use.

(1) Dilute a volume of the infusion to produce a solution containing the equivalent of 0.6% w/v of benzylpenicillin.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dissolve 5 mg of *benzylpenicillin for system suitability EPCRS* in 0.35 mL of *methanol R1* and add 0.65 mL of *water*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC-Pack Pro is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of a 6.8% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.4 with a 50% w/v solution of *orthophosphoric acid*, 30 volumes of *methanol R1* and 60 volumes of *water*.

Mobile phase B 10 volumes of a 6.8% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.4 with a 50% w/v solution of *orthophosphoric acid*, 35 volumes of *water* and 55 volumes of *methanol R1*.

Time (min)	Mobile Phase A (% V/V)	Mobile Phase B (% V/V)	Comment
0 - 7	70	30	isocratic

www.webofpharma.com

https://thuocngocanh.com/

7 - 17	70 → 0	30 → 100	linear gradient
17 - 22	0	100	isocratic

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to benzylpenicillin (retention time, about 7 minutes) are: impurity A, about 0.22; impurity D, about 0.33; impurity C, about 0.35; impurity E, about 0.48 and 0.55; impurity B, about 0.62; impurity F, about 0.81 and 0.83; impurity G, about 1.47; impurity H, about 1.90.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to the epimers of impurity F is at least 1.2;

the *resolution* between the peaks due to impurities D and C is at least 1.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, D, E and F using the chromatogram obtained with solution (3) and multiply the areas of these peaks by the following correction factors: impurity A, 1.3; impurity D, 0.6; impurity E, 2.0; impurity F, 1.7.

In the chromatogram obtained with solution (1);

the sum of the areas of any peaks corresponding to the isomers of impurity E is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the sum of the areas of any peaks corresponding to the epimers of impurity F is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity B is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than 0.75 times the area of the principal peak in the chromatogram obtained with solution (4) (0.15%).

Bacterial endotoxins

Dilute the infusion with *water BET* to contain the equivalent of 10 mg of benzylpenicillin per mL (solution A). The endotoxin limit concentration of solution A is 1.6 IU per mL, Appendix XIV C.

ASSAY

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water* prepared immediately before use.

(1) Dilute a volume of the infusion to produce a solution containing the equivalent of 0.12% w/v of benzylpenicillin.

(2) 0.13% w/v of *benzylpenicillin sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but using isocratic elution, a flow rate of 1.2 mL per minute and an injection volume of 10 µL.

MOBILE PHASE

30 volumes of mobile phase B and 70 volumes of mobile phase A as described under Related substances.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{18}N_2O_4S$ in the infusion using the declared content of $C_{16}H_{17}N_2NaO_4S$ in *benzylpenicillin sodium EPCRS*.

Each mg of $C_{16}H_{17}N_2NaO_4S$ is equivalent to 0.9383 mg of $C_{16}H_{18}N_2O_4S$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of benzylpenicillin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Benzylpenicillin Sodium.

© Crown Copyright 2022

www.webofpharma.com

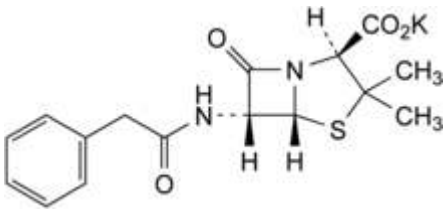
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzylpenicillin Potassium

General Notices

(Ph. Eur. monograph 0113)



$C_{16}H_{17}KN_2O_4S$ 372.5 *113-98-4*

Action and use

Penicillin antibacterial.

Preparation

Benzylpenicillin for Injection

Ph Eur

DEFINITION

Potassium (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Substance produced by the growth of certain strains of *Penicillium notatum* or related organisms.

Content

95.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Very soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuvienthuocngocanh.com/

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *benzylpenicillin potassium CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *water R*.

Reference solution (a) Dissolve 25 mg of *benzylpenicillin potassium CRS* in 5 mL of *water R*.

Reference solution (b) Dissolve 25 mg of *benzylpenicillin potassium CRS* and 25 mg of *phenoxymethylpenicillin potassium CRS* in 5 mL of *water R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube on a water-bath for 1 min; a reddish-brown colour develops.

D. It gives reaction (a) of potassium (2.3.1).

TESTS

pH (2.2.3)

5.5 to 7.5.

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Appearance of solution

The solution is clear (2.2.1).

Dissolve 3.0 g in *water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Test solution (b) Dissolve 80.0 mg of the substance to be examined in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of *benzylpenicillin sodium CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *benzylpenicillin for system suitability CRS* (containing impurities A, B, C, D, E, F, G and H) in 0.35 mL of *methanol R1* and add 0.65 mL of *water R*.

Reference solution (c) Dilute 1.0 mL of test solution (b) to 100.0 mL with *water R*.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 20.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 10 volumes of a 68 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.4 with a 500 g/L solution of *phosphoric acid R*, 30 volumes of *methanol R1* and 60 volumes of *water for chromatography R*;

— *mobile phase B*: mix 10 volumes of a 68 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.4 with a 500 g/L solution of *phosphoric acid R*, 35 volumes of *water for chromatography R* and 55 volumes of *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	70	30
7 - 17	70 → 0	30 → 100
17 - 22	0	100

Flow rate 1.5 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 225 nm.

Injection 20 µL of test solution (b) and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *benzylpenicillin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D, E, F, G and H.

Relative retention With reference to benzylpenicillin (retention time = about 7 min): impurity A = about 0.22; impurity D = about 0.33; impurity C = about 0.35; impurity E = about 0.48 and 0.55; impurity B = about 0.62; impurity F = about 0.81 and 0.83; impurity G = about 1.47; impurity H = about 1.90.

System suitability:

— *resolution*: minimum 1.2 between the peaks due to the epimers of impurity F and minimum 1.5 between the peaks due to impurities D and C in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 20 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.4; impurity D = 0.6; impurity E = 2.0; impurity F = 1.7;

— for each impurity, use the concentration of benzylpenicillin potassium in reference solution (c).

Limits:

— *impurity F*: maximum 2.0 per cent for the sum of the 2 epimers;

— *impurity E*: maximum 1.0 per cent for the sum of the isomers;

— *impurity B*: maximum 0.5 per cent;

— *impurities A, C, D, G, H*: for each impurity, maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 3.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase A, mobile phase B (70:30 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.2 mL/min.

Injection 10 µL of test solution (a) and reference solution (a).

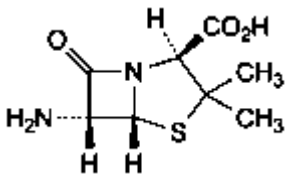
Calculate the percentage content of $C_{16}H_{17}KN_2O_4S$ taking into account the assigned content of *benzylpenicillin sodium CRS* and a conversion factor of 1.045.

STORAGE

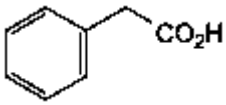
In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

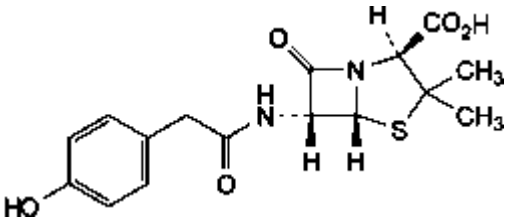
Specified impurities *A, B, C, D, E, F, G, H.*



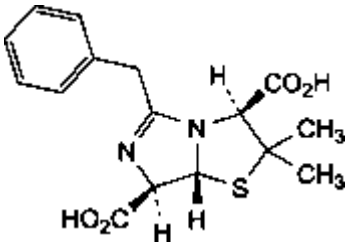
A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



B. phenylacetic acid,



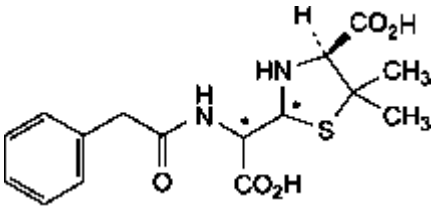
C. (2*S*,5*R*,6*R*)-6-[[(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



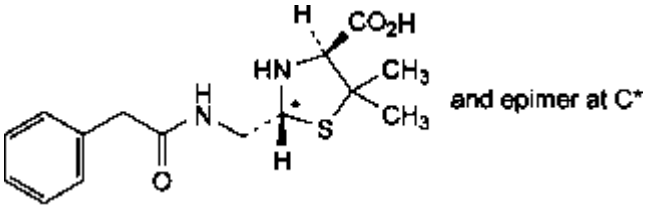
D. (3*S*,7*R*,7a*R*)-5-benzyl-2,2-dimethyl-2,3,7,7a-tetrahydroimidazo[5,1-*b*]thiazole-3,7-dicarboxylic acid (penillic acid of benzylpenicillin),

www.webofpharma.com

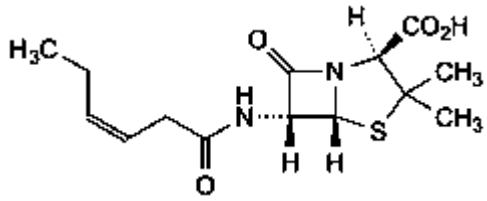
https://thuocngocanh.com/



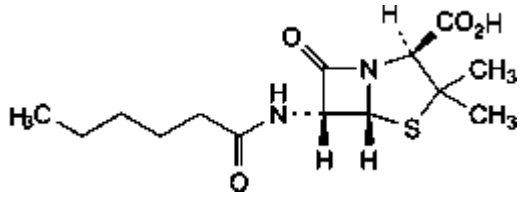
E. (4*S*)-2-[carboxy[(phenylacetyl)amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of benzylpenicillin),



F. (2*RS*,4*S*)-5,5-dimethyl-2-[[(phenylacetyl)amino]methyl]thiazolidine-4-carboxylic acid (penilloic acids of benzylpenicillin),



G. (2*S*,5*R*,6*R*)-6-[(3*Z*)-hex-3-enoylamino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,



H. (2*S*,5*R*,6*R*)-6-(hexanoylamino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (dihydropenicillin F).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

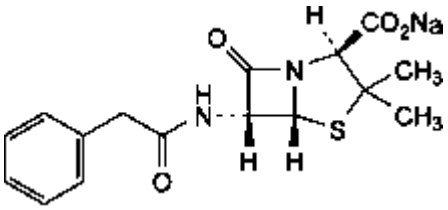
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Benzylpenicillin Sodium

General Notices

(Ph. Eur. monograph 0114)



$C_{16}H_{17}N_2NaO_4S$ 356.4 *69-57-8*

Action and use

Penicillin antibacterial.

Preparations

Benzylpenicillin Eye Drops

Benzylpenicillin for Injection

Benzylpenicillin Infusion

Ph Eur

DEFINITION

Sodium (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Substance produced by the growth of certain strains of *Penicillium notatum* or related organisms.

Content

95.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Very soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *benzylpenicillin sodium CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *water R*.

Reference solution (a) Dissolve 25 mg of *benzylpenicillin sodium CRS* in 5 mL of *water R*.

Reference solution (b) Dissolve 25 mg of *benzylpenicillin sodium CRS* and 25 mg of *phenoxymethylpenicillin potassium CRS* in 5 mL of *water R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is practically colourless. Place the test-tube on a water-bath for 1 min; a reddish-brown colour develops.

D. It gives reaction (a) of sodium (2.3.1).

TESTS

pH (2.2.3)

www.webofpharma.com

https://thuocngocanh.com/

5.5 to 7.5.

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*).

Dissolve 3.0 g in *water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Test solution (b) Dissolve 80.0 mg of the substance to be examined in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of *benzylpenicillin sodium CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *benzylpenicillin for system suitability CRS* (containing impurities A, B, C, D, E, F, G and H) in 0.35 mL of *methanol R1* and add 0.65 mL of *water R*.

Reference solution (c) Dilute 1.0 mL of test solution (b) to 100.0 mL with *water R*.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 20.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 10 volumes of a 68 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.4 with a 500 g/L solution of *phosphoric acid R*, 30 volumes of *methanol R1* and 60 volumes of *water for chromatography R*;

— *mobile phase B*: mix 10 volumes of a 68 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.4 with a 500 g/L solution of *phosphoric acid R*, 35 volumes of *water for chromatography R* and 55 volumes of *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	70	30
7 - 17	70 → 0	30 → 100

www.webofpharma.com

https://thuvienthuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
17 - 22	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL of test solution (b) and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *benzylpenicillin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D, E, F, G and H.

Relative retention With reference to benzylpenicillin (retention time = about 7 min): impurity A = about 0.22; impurity D = about 0.33; impurity C = about 0.35; impurity E = about 0.48 and 0.55; impurity B = about 0.62; impurity F = about 0.81 and 0.83; impurity G = about 1.47; impurity H = about 1.90.

System suitability:

— *resolution*: minimum 1.2 between the peaks due to the epimers of impurity F and minimum 1.5 between the peaks due to impurities D and C in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 20 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.3; impurity D = 0.6; impurity E = 2.0; impurity F = 1.7;

— for each impurity, use the concentration of benzylpenicillin sodium in reference solution (c).

Limits:

— *impurity E*: maximum 2.0 per cent for the sum of the isomers;

— *impurity F*: maximum 1.0 per cent for the sum of the 2 epimers;

— *impurity B*: maximum 0.5 per cent;

— *impurities A, C, D, G, H*: for each impurity, maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 3.0 per cent;

— *reporting threshold*: 0.05 per cent.

2-Ethylhexanoic acid (*2.4.28*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent *m/m*.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase A, mobile phase B (70:30 *V/V*).

Flow rate 1.2 mL/min.

Injection 10 µL of test solution (a) and reference solution (a).

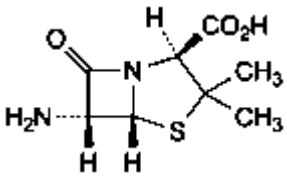
Calculate the percentage content of $C_{16}H_{17}N_2NaO_4S$ taking into account the assigned content of *benzylpenicillin sodium CRS*.

STORAGE

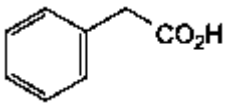
In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

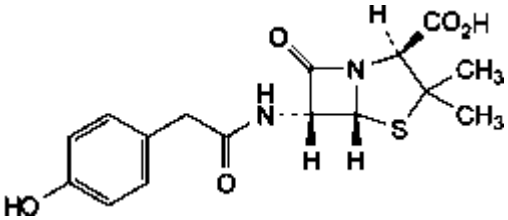
Specified impurities *A, B, C, D, E, F, G, H.*



A. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



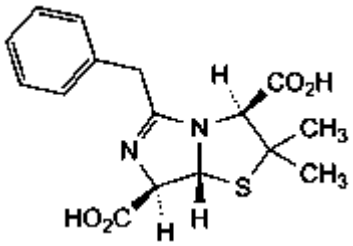
B. phenylacetic acid,



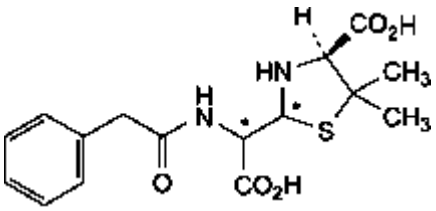
C. (2*S*,5*R*,6*R*)-6-[[(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,

www.webofpharma.com

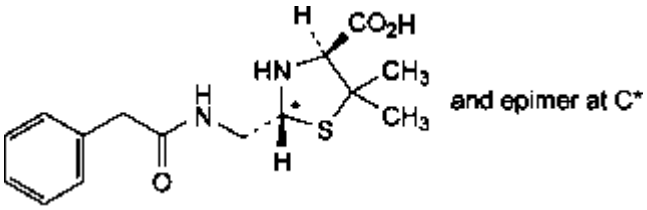
https://thuocngocanh.com/



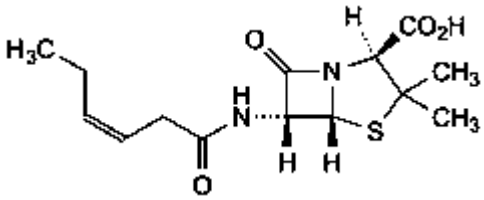
D. (3*S*,7*R*,7a*R*)-5-benzyl-2,2-dimethyl-2,3,7,7a-tetrahydroimidazo[5,1-*b*]thiazole-3,7-dicarboxylic acid (penillic acid of benzylpenicillin),



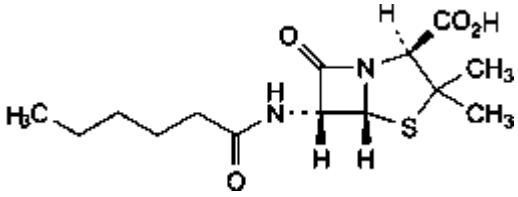
E. (4*S*)-2-[carboxy[(phenylacetyl)amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of benzylpenicillin),



F. (2*RS*,4*S*)-5,5-dimethyl-2-[[(phenylacetyl)amino]methyl]thiazolidine-4-carboxylic acid (penilloic acids of benzylpenicillin),



G. (2*S*,5*R*,6*R*)-6-[(3*Z*)-hex-3-enoylamino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (iso-penicillin F),



H. (2*S*,5*R*,6*R*)-6-(hexanoylamino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (dihydropenicillin F).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

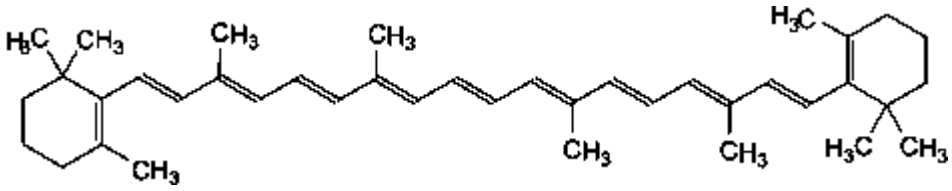
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betacarotene

General Notices

(Ph. Eur. monograph 1069)



$C_{40}H_{56}$ 536.9 *7235-40-7*

Action and use

Precursor of vitamin A.

Ph Eur

DEFINITION

Main component 1,1′-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*,17*E*)-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl]bis(2,6,6-trimethylcyclohexene) (β,β-carotene, betacarotene, *all-trans*-betacarotene, *all-E*-betacarotene).

Content

95.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Brown-red or brownish-red, crystalline powder.

Solubility

Practically insoluble in water, soluble in tetrahydrofuran, practically insoluble in anhydrous ethanol.

It is sensitive to air, heat and light, especially in solution.

IDENTIFICATION

Carry out all operations as rapidly as possible. Prepare the solutions immediately before use.

www.webofpharma.com

https://nhathuocngocanh.com/

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in tetrahydrofuran R and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 50.0 mL with tetrahydrofuran R. Dilute 3.0 mL of this solution to 100.0 mL with cyclohexane R.

Absorption maximum 455 nm.

Shoulder About 427 nm.

Absorbance ratio A_{455}/A_{483} = 1.14 to 1.18.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Carry out all operations as rapidly as possible. Prepare the solutions immediately before use.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

Stabilised tetrahydrofuran tetrahydrofuran R containing 0.25 g/L of butylhydroxytoluene R.

Test solution Dissolve 50.0 mg of the substance to be examined in stabilised tetrahydrofuran and dilute to 200.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with anhydrous ethanol R.

Reference solution (a) Dissolve 50.0 mg of betacarotene CRS in stabilised tetrahydrofuran and dilute to 200.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with anhydrous ethanol R.

Reference solution (b) Dissolve 5 mg of betacarotene for system suitability CRS (containing impurities C, D, E, G and H) in stabilised tetrahydrofuran and dilute to 20 mL with the same solvent. Dilute 1 mL of the solution to 20 mL with anhydrous ethanol R.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with stabilised tetrahydrofuran. Dilute 1.0 mL of this solution to 10.0 mL with anhydrous ethanol R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: amidoalkylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase Dissolve 50 mg of butylhydroxytoluene R in 20 mL of 2-propanol R, then add 0.2 mL of N,N-diisopropylethylamine R, 25 mL of a 2.0 g/L solution of ammonium acetate R, 455 mL of acetonitrile R and 450 mL of methanol R; warm to room temperature and dilute to 1000 mL with methanol R.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 448 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 2.7 times the retention time of betacarotene.

Identification of impurities Use the chromatogram supplied with *betacarotene for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C, D, E, G and H.

Relative retention With reference to betacarotene (retention time = about 28 min): impurity G = about 0.6; impurity C = about 0.95; impurity D = about 1.05; impurity E = about 1.15; impurity H = about 2.4.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity C and betacarotene;

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to betacarotene.

Limits:

— *impurity E*: maximum 4.0 per cent;

— *impurity D*: maximum 2.0 per cent;

— *impurity C*: maximum 0.6 per cent;

— *impurity G*: maximum 0.4 per cent;

— *impurity H*: maximum 0.4 per cent;

— *unspecified impurities*: for each impurity, maximum 0.15 per cent;

— *sum of impurities other than D and E*: maximum 5.0 per cent;

— *reporting threshold*: 0.05 per cent (0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c)).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Loss on drying (*2.2.32*)

Maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 40 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification:

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{40}H_{56}$ taking into account the assigned content of *betacarotene CRS*.

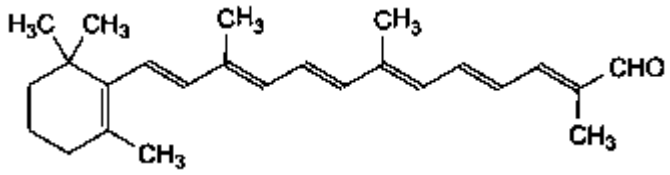
STORAGE

In an airtight container, protected from light.

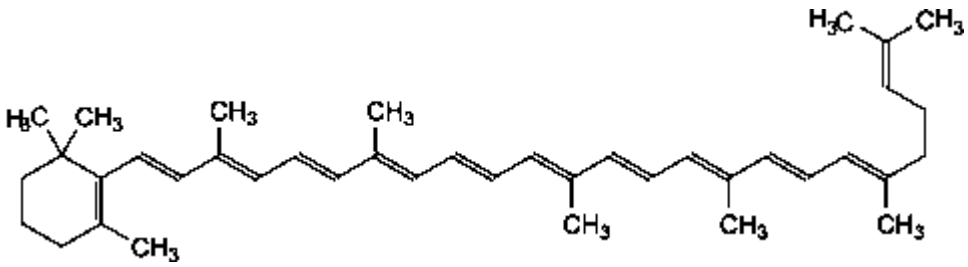
IMPURITIES

Specified impurities *C, D, E, G, H.*

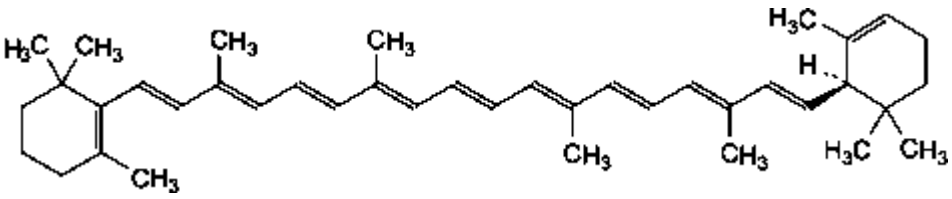
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, F.*



A. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-2,7,11-trimethyl-13-(2,6,6-trimethylcyclohex-1-en-1-yl)trideca-2,4,6,8,10,12-hexaenal (12′-apo-β-caroten-12′-al),



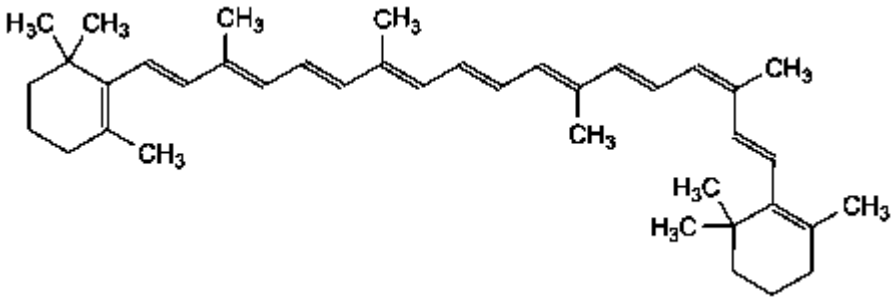
B. 1-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*,17*E*,19*E*)-3,7,12,16,20,24-hexamethylpentacosa-1,3,5,7,9,11,13,15,17,19,23-undecaen-1-yl]-2,6,6-trimethylcyclohexene (β,Ψ-carotene, γ-carotene),



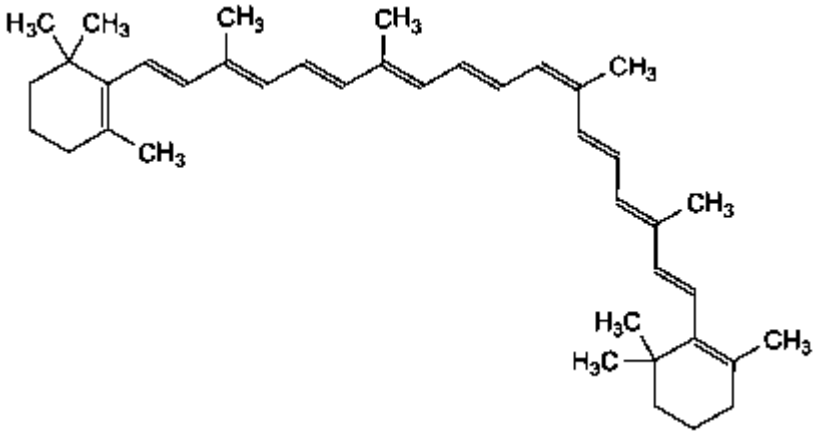
www.webofpharma.com

https://thuocngocanh.com/

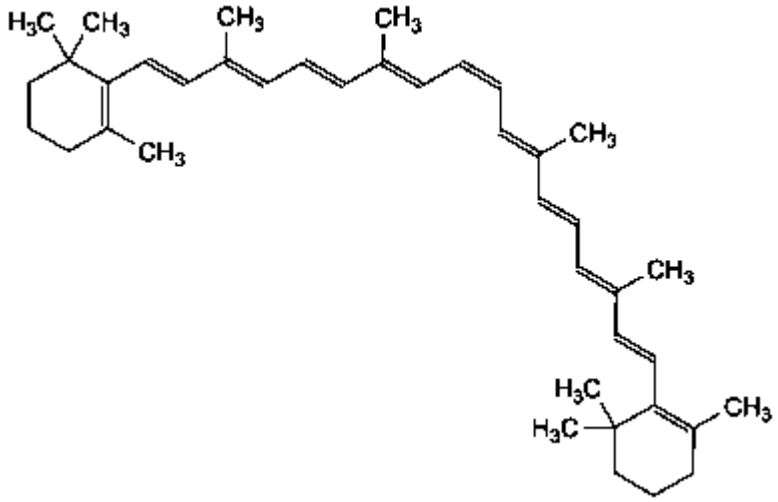
C. 1,3,3-trimethyl-2-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*,17*E*)-3,7,12,16-tetramethyl-18-[(1*R*)-2,6,6-trimethylcyclohex-2-en-1-yl]octadeca-1,3,5,7,9,11,13,15,17-nonaen-1-yl]cyclohexene ((6′*R*)-β,ε-carotene, α-carotene),



D. 1,1′-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*Z*,17*E*)-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl]bis(2,6,6-trimethylcyclohexene) (9-*cis*-β,β-carotene, 9-*cis*-betacarotene),



E. 1,1′-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*Z*,13*E*,15*E*,17*E*)-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl]bis(2,6,6-trimethylcyclohexene) (13-*cis*-β,β-carotene, 13-*cis*-betacarotene),



F. 1,1'-[(1*E*,3*E*,5*E*,7*E*,9*Z*,11*E*,13*E*,15*E*,17*E*)-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl]bis(2,6,6-trimethylcyclohexene) (15-cis-β,β-carotene, 15-*cis*-betacarotene),

G. unknown structure (oxidation products),

H. unknown structure.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

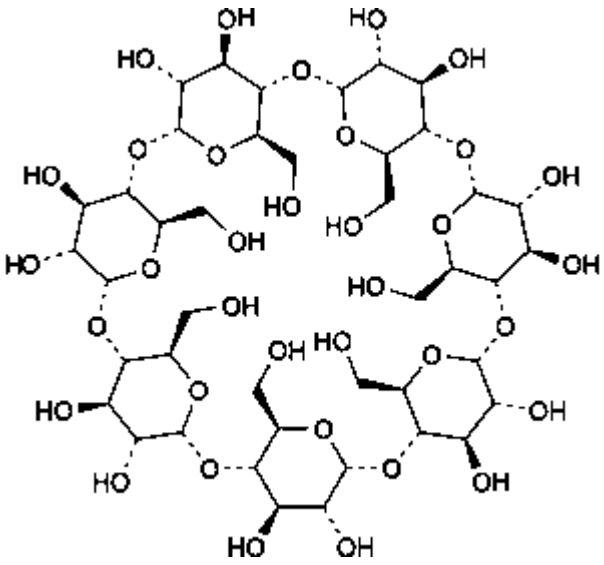
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betadex

General Notices

Betacyclodextrin

(Ph. Eur. monograph 1070)



$[C_6H_{10}O_5]_7$ 1135 *7585-39-9*

Action and use

Carrier molecule for drug delivery systems.

Ph Eur

DEFINITION

Cycloheptakis-(1→4)-(α-D-glucopyranosyl) (cyclomaltoheptaose or β-cyclodextrin).

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, amorphous or crystalline, hygroscopic powder.

Solubility

www.webofpharma.com

https://thietbiduocngocanh.com/

Solubility

Sparingly soluble in water and in propylene glycol, practically insoluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Dissolve 0.2 g in 2 mL of *iodine solution R4* by warming on a water-bath, and allow to stand at room temperature. A yellowish-brown precipitate is formed.

TESTS

Solution S

Dissolve 1.000 g in *carbon dioxide-free water R* with heating, allow to cool and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*).

pH (*2.2.3*)

5.0 to 8.0.

To 10 mL of solution S add 0.1 mL of a saturated solution of *potassium chloride R*.

Specific optical rotation (*2.2.7*)

+ 160 to + 164 (dried substance), determined on solution S.

Reducing sugars

Maximum 0.2 per cent.

Test solution To 1 mL of solution S add 1 mL of *cupri-tartaric solution R4*. Heat on a water-bath for 10 min, cool to room temperature. Add 10 mL of *ammonium molybdate reagent R1* and allow to stand for 15 min.

Reference solution Prepare a reference solution at the same time and in the same manner as the test solution, using 1 mL of a 0.02 g/L solution of *glucose R*.

Measure the absorbance (*2.2.25*) of the test solution and the reference solution at the absorption maximum at 740 nm using *water R* as the compensation liquid. The absorbance of the test solution is not greater than that of the reference solution.

Light-absorbing impurities

www.webofpharma.com

https://thuocngocanh.com/

Examine solution S between 230 nm and 750 nm. Between 230 nm and 350 nm, the absorbance (2.2.25) is not greater than 0.10. Between 350 nm and 750 nm, the absorbance (2.2.25) is not greater than 0.05.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.250 g of the substance to be examined in *water R* with heating, cool and dilute to 25.0 mL with the same solvent.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with *water R*.

Reference solution (a) Dissolve 25.0 mg of *alfadex CRS* (impurity A), 25.0 mg of *gammacyclodextrin CRS* (impurity B) and 50.0 mg of *betadex CRS* in *water R*, then dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with *water R*.

Reference solution (c) Dissolve 25.0 mg of *betadex CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase *methanol R*, *water for chromatography R* (10:90 *V/V*).

Flow rate 1.5 mL/min.

Detection Differential refractometer.

Equilibration With the mobile phase for about 3 h.

Injection 50 µL of test solution (a) and reference solutions (a) and (b).

Run time 1.5 times the retention time of betadex.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B.

Relative retention With reference to betadex (retention time = about 10 min): impurity B = about 0.3; impurity A = about 0.45.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities B and A; if necessary, adjust the concentration of methanol in the mobile phase.

Calculation of percentage contents:

— for impurities A and B, use the concentration of the corresponding impurity in reference solution (b);

www.webofpharma.com

https://thuocngocanh.com/

— for impurities other than A and B, use the concentration of betadex in reference solution (b).

Limits:

— *impurities A, B*: for each impurity, maximum 0.25 per cent;

— *sum of impurities other than A and B*: maximum 0.5 per cent;

— *reporting threshold*: 0.15 per cent.

Residual solvents

Head-space gas chromatography (2.2.28): use the standard additions method.

Internal standard *ethylene chloride R*.

Stock solution A To 20 µL of *ethylene chloride R* add 0.5 mL of *dimethyl sulfoxide R* and dilute to 25.0 mL with *water R*.

Stock solution B To 25 µL of *trichloroethylene R* add 25 µL of *toluene R* and 0.5 mL of *dimethyl sulfoxide R*, then dilute to 50.0 mL with *water R*.

Test solutions (a), (b), (c) and (d) In each of 4 identical vials, introduce 0.5 g of the substance to be examined, 0.10 g of *calcium chloride R*, 30 µL of *α-amylase solution R* and 1 mL of reference solutions (a), (b), (c) and (d), respectively, then add 9.0 mL of *water R*. Prepare test solutions (b), (c) and (d) in triplicate.

Reference solution (a) Dilute 250 µL of stock solution A to 10.0 mL with *water R*.

Reference solution (b) To 100 µL of stock solution B add 250 µL of stock solution A and dilute to 10.0 mL with *water R*.

Reference solution (c) To 200 µL of stock solution B add 250 µL of stock solution A and dilute to 10.0 mL with *water R*.

Reference solution (d) To 300 µL of stock solution B add 250 µL of stock solution A and dilute to 10.0 mL with *water R*.

Blank solution In a vial identical to those used for the test solutions, introduce 0.10 g of *calcium chloride R*, 30 µL of *α-amylase solution R*, 0.5 mL of *dimethyl sulfoxide R* and 10.0 mL of *water R*.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.7 mL/min.

Static head-space conditions that may be used: if the equipment has different setting parameters, adjust the equipment settings so as to comply with the system suitability criterion:

www.webofpharma.com

https://thuocngocanh.com/

— *equilibration temperature*: 45 °C;

— *equilibration time*: 2 h;

— *syringe temperature*: 50 °C;

— *injection speed*: 500 µL/s.

Temperature:

— *column*: 50 °C;

— *injection port*: 140 °C;

— *detector*: 280 °C.

Detection Flame ionisation.

Injection 200 µL.

Relative retention With reference to the internal standard (retention time = about 13 min): trichloroethylene = about 0.6; toluene = about 0.8.

System suitability Test solutions (b), (c) and (d):

— *repeatability*: maximum relative standard deviations of the ratios of the areas of the peaks due to trichloroethylene and toluene to that of the peak due to ethylene chloride of 10.0 per cent, for each set of triplicate test solutions and each residual solvent.

Calculate the content of trichloroethylene and of toluene taking their relative densities to be 1.46 and 0.87, respectively.

Limits:

— *trichloroethylene*: maximum 10 ppm;

— *toluene*: maximum 10 ppm.

Loss on drying (2.2.32)

Maximum 16.0 per cent, determined on 1.000 g by drying in an oven at 120 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solutions (a) and (c).

www.webofpharma.com

https://thuvienthuocngocanh.com/

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the area of the peak due to betadex, determined on 5 injections.

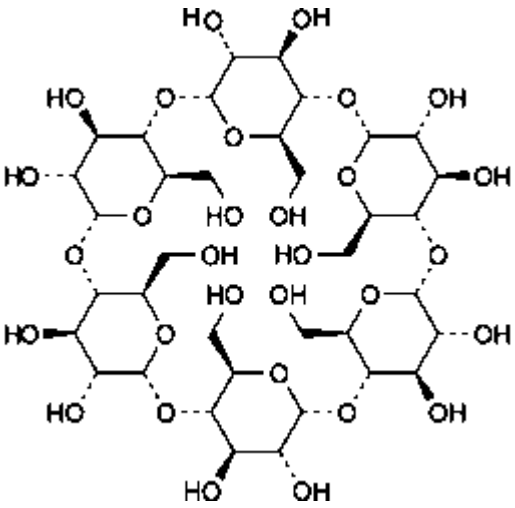
Calculate the percentage content of $[C_6H_{10}O_5]_7$ using the chromatogram obtained with reference solution (c) and taking into account the assigned content of *betadex CRS*.

STORAGE

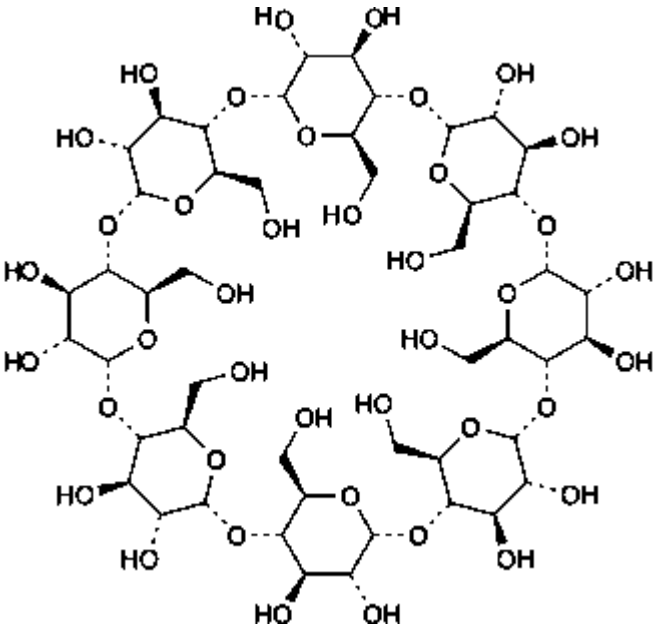
In an airtight container.

IMPURITIES

Specified impurities *A, B.*



A. cyclohexakis-(1→4)-(α-D-glucopyranosyl) (alfadex or cyclomaltohexaose or α-cyclodextrin),



www.webofpharma.com

https://thuvienthuocngocanh.com/

B. cyclooctakis-(1→4)-(α-D-glucopyranosyl) (cyclomaltooctaose or γ-cyclodextrin).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

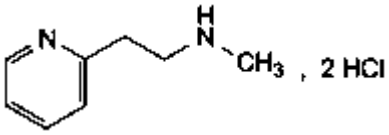
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betahistine Dihydrochloride

General Notices

(Ph. Eur. monograph 1665)



$C_8H_{14}Cl_2N_2$ 209.1 *5579-84-0*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Preparation

Betahistine Dihydrochloride Tablets

Ph Eur

DEFINITION

N-Methyl-2-(pyridin-2-yl)ethanamine dihydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow powder, very hygroscopic.

Solubility

Very soluble in water, soluble in ethanol (96 per cent), practically insoluble in 2-propanol.

IDENTIFICATION

First identification: B, D.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, C, D.

A. Melting point (2.2.14): 150 °C to 154 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *betahistine dihydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 2 mL of *ethanol (96 per cent) R*.

Reference solution Dissolve 10 mg of *betahistine dihydrochloride CRS* in 2 mL of *ethanol (96 per cent) R*.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *concentrated ammonia R*, *ethyl acetate R*, *methanol R* (0.75:15:30 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying At 110 °C for 10 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R*, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_8 (2.2.2. *Method II*).

pH (2.2.3)

2.0 to 3.0 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 10 mg of *betahistine dihydrochloride CRS* and 10 mg of *2-vinylpyridine R* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 2.0 mL of reference solution (b) to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 2.0 g of *sodium dodecyl sulfate R* in a mixture of 15 mL of a 10 per cent *V/V* solution of *sulfuric acid R*, 35 mL of a 17 g/L solution of *tetrabutylammonium hydrogen sulfate R* and 650 mL of *water R*; adjust to pH 3.3 using *dilute sodium hydroxide solution R* and mix with 300 mL of *acetonitrile R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL.

Run time 4 times the retention time of betahistine.

Relative retention With reference to betahistine (retention time = about 7 min): impurity B = about 0.2; impurity A = about 0.3; impurity C = about 3.

System suitability Reference solution (a):

— *resolution*: minimum 3.5 between the peaks due to 2-vinylpyridine and betahistine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.4;

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times of the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 80.0 mg in 50 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added to reach the second point of inflexion.

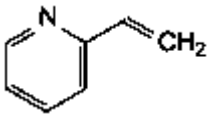
1 mL of *0.1 M sodium hydroxide* is equivalent to 10.46 mg of $C_8H_{14}Cl_2N_2$.

STORAGE

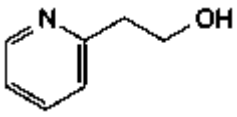
In an airtight container.

IMPURITIES

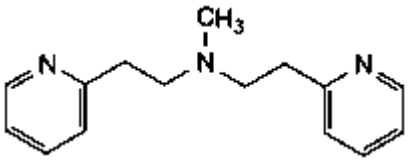
Specified impurities *A, B, C.*



A. 2-ethenylpyridine (2-vinylpyridine),



B. 2-(pyridin-2-yl)ethanol,



C. *N*-methyl-2-(pyridin-2-yl)-*N*-[2-(pyridin-2-yl)ethyl]ethanamine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betahistine Dihydrochloride Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Betahistine Dihydrochloride Tablets contain Betahistine Dihydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of betahistine dihydrochloride, $C_8H_{12}N_2,2HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 5 mg of Betahistine Dihydrochloride with 100 mL of *water* and filter. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits a maximum at about 260 nm, a less well-defined maximum at about 267 nm and a shoulder at about 256 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of the mobile phase to a quantity of the powdered tablets containing 32 mg of Betahistine Dihydrochloride, shake for 10 minutes, add sufficient mobile phase to produce 100 mL, mix, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 500 volumes with the mobile phase.

(3) 0.00064% w/v of N-*methyl-2-(pyridin-2-yl)*-N-*[2-(pyridine-2-yl)ethyl]ethanamine trihydrochloride BPCRS* in the mobile phase.

(4) 0.000032% w/v of *2-vinylpyridine* in *acetonitrile*.

(5) 0.00064% w/v each of N-*methyl-2-(pyridin-2-yl)*-N-*[2-(pyridine-2-yl)ethyl]ethanamine trihydrochloride BPCRS* and *betahistine dihydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax XDB Eclipse is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for four times the retention time of betahistine (retention time of betahistine, about 5 minutes).

MOBILE PHASE

Dissolve 0.4 g of *hexylamine* in 600 mL of a solution containing 0.46% w/v of *sodium dihydrogen orthophosphate monohydrate* and 0.27% w/v of *sodium dodecyl sulfate*, add 400 mL of *acetonitrile*, mix and adjust the pH to 3.5 using *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution factor* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to *N*-methyl-bis[β-(2-pyridyl)ethyl]amine is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (2%);

the area of any peak corresponding to 2-vinylpyridine is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of the peaks corresponding to *N*-methyl-bis[β-(2-pyridyl)ethyl]amine, 2-vinylpyridine and any other *secondary peaks* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than 0.05% of that of the principal peak in the chromatogram obtained with solution (1) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of the mobile phase to a quantity of the powdered tablets containing 32 mg of Betahistine Dihydrochloride, shake for 10 minutes, add sufficient mobile phase to produce 100 mL, mix, centrifuge and use the supernatant liquid.

(2) 0.032% w/v of *betahistine dihydrochloride BPCRS* in the mobile phase.

(3) 0.00064% w/v each of N-*methyl-2-(pyridin-2-yl)*-N-*[2-(pyridine-2-yl)ethyl]ethanamine trihydrochloride BPCRS* and *betahistine dihydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.0.

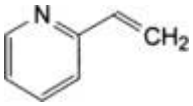
DETERMINATION OF CONTENT

Calculate the content of $C_8H_{12}N_2,2HCl$ in the tablets using the declared content of $C_8H_{12}N_2,2HCl$ in *betahistine dihydrochloride BPCRS*.

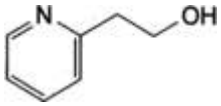
STORAGE

Betahistine Dihydrochloride Tablets should be protected from light and moisture.

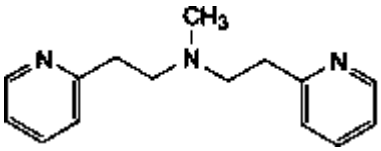
IMPURITIES



1. 2-ethenylpyridine (2-vinylpyridine),



2. 2-(pyridin-2-yl)ethanol,



3. *N*-methyl-2-(pyridin-2-yl)-*N*-[2-(pyridin-2-yl)ethyl]ethanamine.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

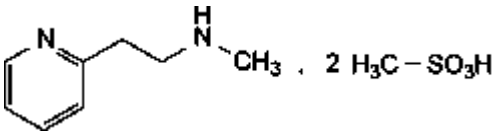
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betahistine Mesilate

General Notices

(Ph. Eur. monograph 1071)



$C_{10}H_{20}N_2O_6S_2$ 328.4 *54856-23-4*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

N-Methyl-2-(pyridin-2-yl)ethanamine bis(methanesulfonate).

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in betahistine mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

White or almost white, crystalline powder, very hygroscopic.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), very slightly soluble in 2-propanol.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (2.2.14): 108 °C to 112 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *betahistine mesilate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *ethanol (96 per cent) R* and dilute to 2 mL with the same solvent.

Reference solution Dissolve 10 mg of *betahistine mesilate CRS* in *ethanol (96 per cent) R* and dilute to 2 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *ethyl acetate R*, *methanol R* (0.75:15:30 *V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying At 110 °C for 10 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. To 0.1 g add 5 mL of *dilute hydrochloric acid R* and shake for about 5 min. Add 1 mL of *barium chloride solution R1*. The solution remains clear. To a further 0.1 g add 0.5 g of *anhydrous sodium carbonate R*, mix and ignite until a white residue is obtained. Allow to cool and dissolve the residue in 7 mL of *water R*. The solution gives reaction (a) of sulfates (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* prepared from *distilled water R*, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

www.webofpharma.com

https://thuocngocanh.com/

2.0 to 3.0 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 10 mg of *betahistine mesilate CRS* and 10 mg of *2-vinylpyridine R* (impurity A) in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 2.0 mL of reference solution (b) to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 2.0 g of *sodium dodecyl sulfate R* in a mixture of 15 volumes of a 10 per cent *V/V* solution of *sulfuric acid R*, 35 volumes of a 17 g/L solution of *tetrabutylammonium hydrogen sulfate R* and 650 volumes of *water R*; adjust to pH 3.3 using *dilute sodium hydroxide solution R* and mix with 300 volumes of *acetonitrile R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL.

Run time 3 times the retention time of betahistine mesilate.

Retention time Betahistine mesilate = about 8 min.

System suitability Reference solution (a):

— *resolution*: minimum 3.5 between the peaks due to impurity A and betahistine mesilate.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

www.webofpharma.com

https://thuocngocanh.com/

2-Propanol (*2.4.24*)

Maximum 0.5 per cent.

Chlorides (*2.4.4*)

Maximum 35 ppm.

To 14 mL of solution S add 1 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 250 ppm.

Dilute 6 mL of solution S to 15 mL with *distilled water R*.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.50 g.

ASSAY

Dissolve 0.140 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

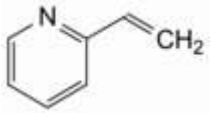
1 mL of *0.1 M perchloric acid* is equivalent to 16.42 mg of $C_{10}H_{20}N_2O_6S_2$.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities A.



A. 2-ethenylpyridine (2-vinylpyridine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

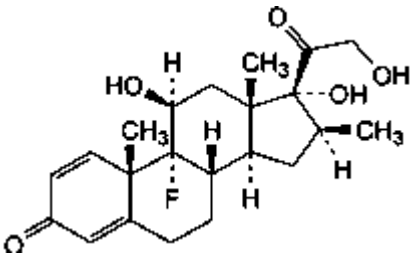
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone

General Notices

(Ph. Eur. monograph 0312)



$C_{22}H_{29}FO_5$ 392.5 *378-44-9*

Action and use

Glucocorticoid.

Preparation

Betamethasone Tablets

Ph Eur

DEFINITION

9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in anhydrous ethanol, very slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison betamethasone CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of methylene chloride R, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of betamethasone CRS in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate TLC silica gel F_{254} plate R.

Mobile phase methanol R, methylene chloride R (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of 2,4-dihydroxybenzaldehyde R in glacial acetic acid R, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of sulfuric acid R and 37.5 mL of glacial acetic acid R; heat at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Add about 2 mg to 2 mL of sulfuric acid R and shake to dissolve. Within 5 min, a deep reddish-brown colour develops. Add this solution to 10 mL of water R and mix. The colour is discharged and a clear solution remains.

TESTS

Specific optical rotation (2.2.7)

+ 118 to + 126 (dried substance).

Dissolve 0.125 g in methanol R and dilute to 25.0 mL with the same solvent.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in a mixture of equal volumes of acetonitrile R and methanol R and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 2 mg of betamethasone CRS and 2 mg of methylprednisolone CRS in mobile phase A and dilute to 100 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: mix 250 mL of acetonitrile R and 700 mL of water for chromatography R and allow to equilibrate; dilute to 1000 mL with water for chromatography R and mix;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 40	100 → 0	0 → 100
40 - 41	0 → 100	100 → 0
41 - 46	100	0

Flow rate 2.5 mL/min.

Detection Spectrophotometer at 254 nm.

Equilibration With mobile phase B for at least 30 min and then with mobile phase A for 5 min; for subsequent chromatograms, use the conditions described from 40 min to 46 min.

Injection 20 µL; inject a mixture of equal volumes of acetonitrile R and methanol R as a blank.

Retention time Methylprednisolone = about 11.5 min; betamethasone = about 12.5 min.

System suitability Reference solution (a):

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *resolution*: minimum 1.5 between the peaks due to methylprednisolone and betamethasone; if necessary, adjust the concentration of acetonitrile in mobile phase A.

Limits:

— *impurities A, B, C, D, E, F, G, H, I, J*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent), and not more than 1 such peak has an area greater than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 238.5 nm.

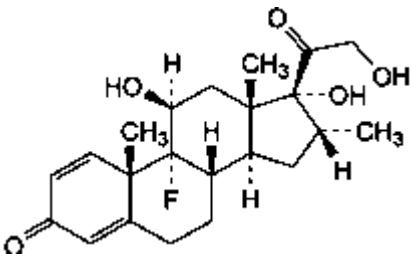
Calculate the content of $C_{22}H_{29}FO_5$ taking the specific absorbance to be 395.

STORAGE

Protected from light.

IMPURITIES

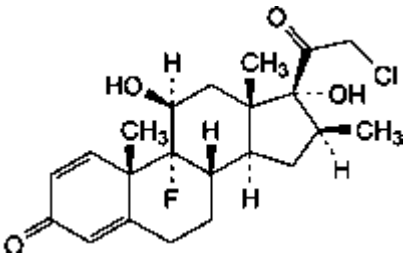
Specified impurities *A, B, C, D, E, F, G, H, I, J.*



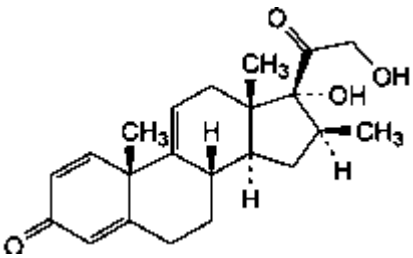
A. 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (dexamethasone),

www.webofpharma.com

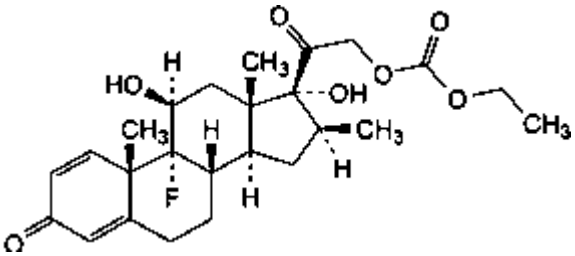
https://thuocngocanh.com/



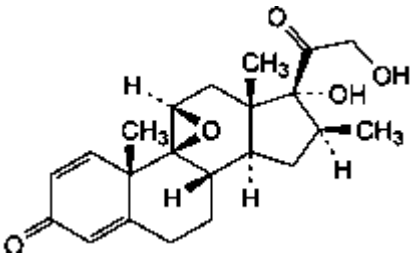
B. 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione,



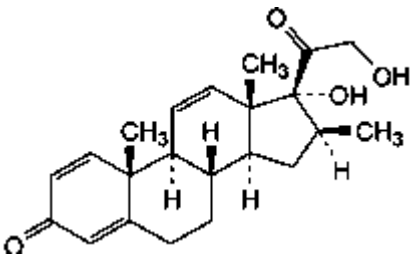
C. 17,21-dihydroxy-16β-methylpregna-1,4,9(11)-triene-3,20-dione,



D. 9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl ethoxycarboxylate,



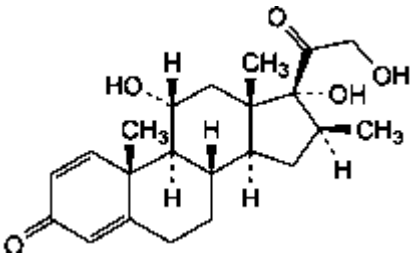
E. 9,11β-epoxy-17,21-dihydroxy-16β-methyl-9β-pregna-1,4-diene-3,20-dione,



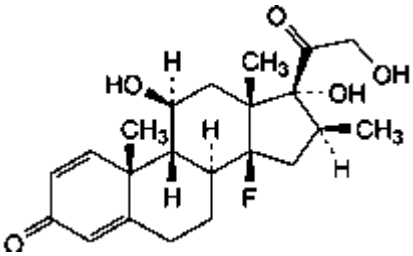
F. 17,21-dihydroxy-16β-methylpregna-1,4,11-triene-3,20-dione,

www.webofpharma.com

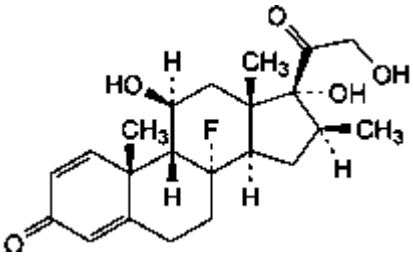
https://thuocngocanh.com/



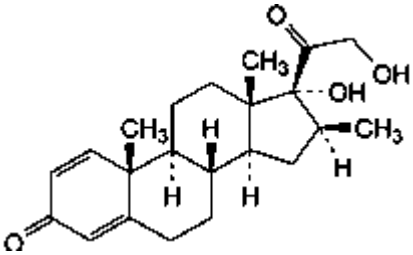
G. 11α,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione,



H. 14-fluoro-11β,17,21-trihydroxy-16β-methyl-8α,9β,14β-pregna-1,4-diene-3,20-dione,



I. 8-fluoro-11β,17,21-trihydroxy-16β-methyl-8α,9β-pregna-1,4-diene-3,20-dione,



J. 17,21-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

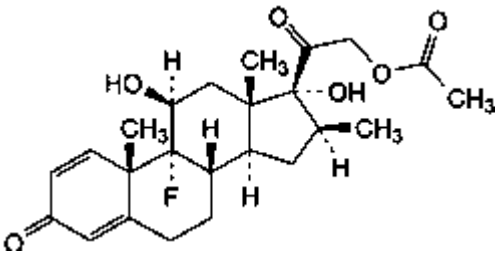
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Acetate

General Notices

(Ph. Eur. monograph 0975)



$C_{24}H_{31}FO_6$ 434.5 *987-24-6*

Action and use

Glucocorticoid.

Ph Eur

DEFINITION

9-Fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate.

Content

97.0 per cent to 103.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, B.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *betamethasone acetate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methanol R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *betamethasone acetate CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a deep reddish-brown colour develops. Add this solution to 10 mL of *water R* and mix. The colour is discharged and a clear solution remains.

TESTS

Specific optical rotation (2.2.7)

+ 120 to + 128 (anhydrous substance).

Dissolve 0.250 g in *dioxan R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in 4 mL of *acetonitrile R* and dilute to 10.0 mL with the same solvent.

www.webofpharma.com

https://nhathuocngocanh.com/

Reference solution (a) Dissolve 2 mg of *betamethasone acetate CRS* and 2 mg of *dexamethasone acetate CRS* (impurity B) in the mobile phase and dilute to 100 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 380 mL of *acetonitrile R* and 550 mL of *water for chromatography R* and allow to equilibrate; dilute to 1000 mL with *water for chromatography R* and mix.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 2.5 times the retention time of betamethasone acetate.

Retention time Betamethasone acetate = about 19 min; impurity B = about 22 min.

System suitability Reference solution (a):

— *resolution*: minimum 3.3 between the peaks due to betamethasone acetate and impurity B; if necessary, adjust slightly the concentration of acetonitrile in the mobile phase.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *total*: not more than 1.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.25 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.100 g.

ASSAY

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 240 nm.

Calculate the content of $C_{24}H_{31}FO_6$ taking the specific absorbance to be 350.

www.webofpharma.com

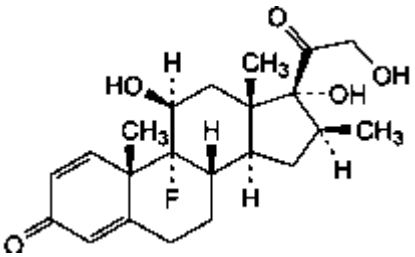
https://thuocngocanh.com/

STORAGE

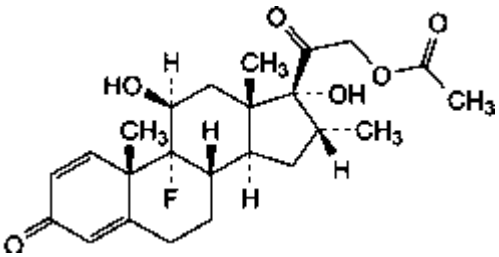
Protected from light.

IMPURITIES

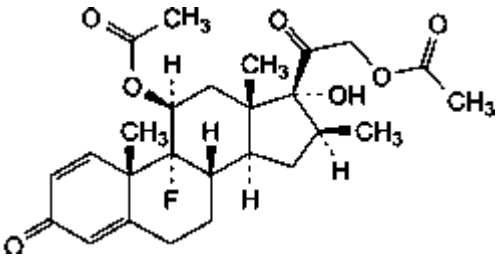
Specified impurities *A, B, C, D.*



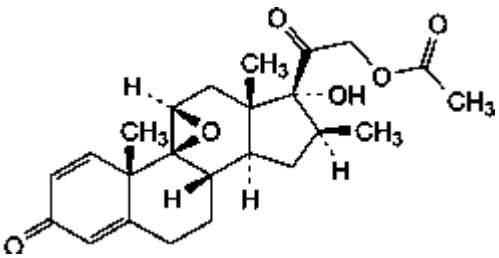
A. 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (betamethasone),



B. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (dexamethasone acetate),



C. 9-fluoro-17-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-11β,21-diyl diacetate (betamethasone 11,21-diacetate),



D. 9,11β-epoxy-17-hydroxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-dien-21-yl acetate.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone and Clioquinol Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone and Clioquinol Cream contains Betamethasone Valerate and Clioquinol, the latter in *very fine powder*, in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

90.0 to 110.0% of the stated amount.

Content of clioquinol, C_9H_5ClINO

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the preparation being examined containing the equivalent of 0.5 mg of betamethasone in 20 mL of *methanol (80%)* by heating on a water bath until the methanol begins to boil. Shake vigorously, cool in ice and centrifuge. Transfer 10 mL of the supernatant liquid to a separating funnel, add 3 mL of *water* and 5 mL of *chloroform*, shake vigorously, allow the layers to separate and evaporate the chloroform layer to dryness in a current of *nitrogen* with gentle heating. Dissolve the residue in 1 mL of *chloroform*.

(2) 0.03% w/v of *betamethasone valerate BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 105° for 5 minutes and spray while hot with *alkaline tetrazolium blue solution*.

MOBILE PHASE

5 volumes of *absolute ethanol*, 10 volumes of *acetone* and 100 volumes of *chloroform*.

CONFIRMATION

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay for betamethasone the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to betamethasone valerate in the chromatogram obtained with solution (3).

C. In the Assay for clioquinol the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to clioquinol in the chromatogram obtained with solution (2).

ASSAY

For betamethasone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the cream containing the equivalent of 2 mg of betamethasone with 100 mL of hot *hexane* for 2 minutes, cool, extract the mixture with 20 mL of *ethanol (96%)* and filter the lower, ethanolic layer through absorbent cotton previously washed with *ethanol (75%)*. Repeat the extraction of the hexane mixture with two 10-mL quantities of *ethanol (75%),* filtering each extract in turn through the absorbent cotton and dilute the combined filtrates to 50 mL with *ethanol (75%)*.

(2) Prepared in the same manner as solution (1) but add 5 mL of a 0.072% w/v solution of *beclometasone dipropionate BPCRS* (internal standard) in *ethanol (80%)* before diluting to 50 mL.

(3) Mix 2 volumes of a solution containing 0.024% w/v of *betamethasone valerate BPCRS* and 0.0012% w/v of *betamethasone 21-valerate BPCRS* in *ethanol (80%)* with 1 volume of a 0.072% w/v solution of the internal standard in *ethanol (80%)* and dilute to 10 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

42 volumes of *absolute ethanol* and 58 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to betamethasone valerate (retention time about 5 minutes) and betamethasone 21-valerate (retention time about 7 minutes) is more than 1.0, if necessary adjust the mixture of *absolute ethanol* and *water* in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the cream using the declared content of $C_{22}H_{29}FO_5$ in *betamethasone valerate BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

For clioquinol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 80 mL of a hot 80% v/v solution of *2-methoxyethanol* to a quantity of the cream containing 30 mg of Clioquinol and heat on a water bath for 5 minutes, swirling vigorously. Cool to room temperature, dilute to 100 mL with the same solvent, mix and filter. To 5 mL of the filtrate add 1 mL of a solution containing 1% w/v of *nickel(II) chloride hexahydrate* and dilute to 50 mL with the mobile phase.

(2) Mix 5 mL of a solution containing 0.024% w/v of *clioquinol BPCRS* in an 80% v/v solution of *2-methoxyethanol* and 1 mL of a solution containing 1% w/v of *nickel(II) chloride hexahydrate* in *water* and dilute to 50 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenyl silica gel for chromatography* (5 µm) (Spherisorb Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 273 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.024% w/v of *nickel(II) chloride hexahydrate* in a mixture of 2 volumes of *methanol*, 3 volumes of *acetonitrile* and 5 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of C_9H_5ClINO in the cream using the declared content of C_9H_5ClINO in *clioquinol BPCRS*.

STORAGE

Betamethasone and Clioquinol Cream should be protected from light.

LABELLING

The quantity of active ingredient with respect to Betamethasone Valerate is stated in terms of the equivalent amount of betamethasone.

© Crown Copyright 2022

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone and Clioquinol Ointment

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone and Clioquinol Ointment contains Betamethasone Valerate and Clioquinol, the latter in *very fine powder*, in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

90.0 to 110.0% of the stated amount.

Content of clioquinol, C_9H_5ClINO

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the ointment containing the equivalent of 1 mg of betamethasone with 10 mL of *methanol* by heating on a water bath until the methanol begins to boil. Shake vigorously, cool in ice and filter. Evaporate the filtrate to dryness in a current of nitrogen and dissolve the residue in 0.5 mL of *chloroform*.

(2) 0.24% w/v of *betamethasone valerate BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 105° for 5 minutes and spray while hot with *alkaline tetrazolium blue solution*.

MOBILE PHASE

5 volumes of *absolute ethanol*, 10 volumes of *acetone* and 100 volumes of *chloroform*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay for betamethasone the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to betamethasone valerate in the chromatogram obtained with solution (3).

C. In the Assay for clioquinol the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to clioquinol in the chromatogram obtained with solution (2).

ASSAY

For betamethasone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing the equivalent of 2 mg of betamethasone in 100 mL of hot *hexane*, cool, extract with 20 mL of *ethanol (65%)* and filter the lower, ethanolic layer through absorbent cotton previously washed with *ethanol (65%)*; repeat the extraction of the hexane mixture with two 10-mL quantities of *ethanol (65%)*, filtering each extract in turn through the absorbent cotton. To the combined extracts, add 5 mL of a 0.072% w/v solution of *beclometasone dipropionate BPCRS* (internal standard) in *ethanol (65%)* and dilute the combined filtrates to 50 mL with *ethanol (65%)*.

(2) Prepare in the same manner as solution (1) but do not add the internal standard before diluting to 50 mL.

(3) Mix 10 mL of a solution containing 0.024% w/v of *betamethasone valerate BPCRS* and 0.0012% w/v of *betamethasone 21-valerate BPCRS* in *ethanol (65%)* with 5 mL of a 0.072% w/v solution of *beclometasone dipropionate BPCRS* (internal standard) in *ethanol (65%)* and dilute to 50 mL with *ethanol (65%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 60°C.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of *absolute ethanol* and *water* adjusted so that the *resolution factor* between the peaks due to betamethasone valerate (retention time about 5 minutes) and betamethasone 21-valerate (retention time about 7 minutes) is greater than 1.0 (a mixture of 42 volumes of *absolute ethanol* and 58 volumes of *water* is usually suitable).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to betamethasone valerate and betamethasone 21-valerate is greater than 1.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{22}H_{29}FO_5$ in the ointment using the declared content of $C_{22}H_{29}FO_5$ in *betamethasone valerate BPCRS* and using peak areas.

For clioquinol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 80 mL of a hot 80% v/v solution of *2-methoxyethanol* to a quantity of the cream containing 30 mg of Clioquinol and heat on a water bath for 5 minutes, swirling vigorously. Cool to room temperature, dilute to 100 mL with the same solvent, mix and filter. To 5 mL of the filtrate add 1 mL of a solution containing 1% w/v of *nickel(II) chloride hexahydrate* and dilute to 50 mL with the mobile phase.

(2) Mix 5 mL of a solution containing 0.024% w/v of *clioquinol BPCRS* in an 80% v/v solution of *2-methoxyethanol* and 1 mL of a solution containing 1% w/v of *nickel(II) chloride hexahydrate* in *water* and dilute to 50 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with particles of silica, the surface of which has been modified with chemically bonded phenyl groups (5 µm) (Spherisorb Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 273 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A solution containing 0.024% w/v of *nickel(II) chloride hexahydrate* in a mixture of 2 volumes of *methanol*, 3 volumes of *acetonitrile* and 5 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of C_9H_5ClINO in the cream using the declared content of C_9H_5ClINO in *clioquinol BPCRS*.

STORAGE

Betamethasone and Clioquinol Ointment should be protected from light.

LABELLING

The quantity of active ingredient with respect to Betamethasone Valerate is stated in terms of the equivalent amount of betamethasone.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

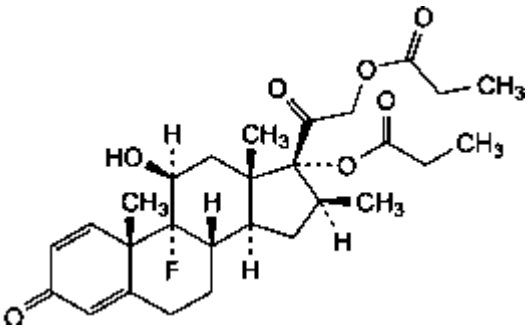
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Dipropionate

General Notices

(Ph. Eur. monograph 0809)



$C_{28}H_{37}FO_7$ 504.6 *5593-20-4*

Action and use

Glucocorticoid.

Preparations

Calcipotriol and Betamethasone Cutaneous Foam

Calcipotriol and Betamethasone Gel

Calcipotriol and Betamethasone Ointment

Ph Eur

DEFINITION

9-Fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *betamethasone dipropionate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *betamethasone dipropionate CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat the plate at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a deep reddish-brown colour develops. Add this solution to 10 mL of *water R* and mix. The colour is discharged and a clear solution remains.

TESTS

Specific optical rotation (2.2.7)

+ 84 to + 88 (dried substance).

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Dissolve 60.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *betamethasone dipropionate for system suitability A CRS* (containing impurities B, C, D, E, G and I) in the mobile phase and dilute to 2 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 60.0 mg of *betamethasone dipropionate CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 5 mg of *betamethasone dipropionate for peak identification CRS* (containing impurity H) in the mobile phase and dilute to 2 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 2.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (2.5 µm);

— *temperature*: 20 ± 2 °C.

Mobile phase Mix 35 mL of *water for chromatography R* and 56 mL of *acetonitrile R* and allow to equilibrate; dilute to 100 mL with *water for chromatography R* and mix.

Flow rate 0.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 5 µL of test solution (a) and reference solutions (a), (b) and (d).

Run time 3 times the retention time of betamethasone dipropionate.

Identification of impurities Use the chromatogram supplied with *betamethasone dipropionate for system suitability A CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, C, D, E, G and I; use the chromatogram supplied with *betamethasone dipropionate for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity H.

Relative retention With reference to betamethasone dipropionate (retention time = about 10 min): impurity B = about 0.4; impurity C = about 0.5; impurity D = about 0.7; impurity I = about 1.16; impurity E = about 1.22; impurity H = about 1.7; impurity G = about 2.1.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate; minimum 4.0, where

www.webofpharma.com

https://thietbiuocngocanh.com/

H_p = height above the baseline of the peak due to impurity I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity E.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity G = 1.3; impurity H = 1.4;

— *impurity C*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities B, H*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities D, E, G*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity I*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{28}H_{37}FO_7$ taking into account the assigned content of *betamethasone dipropionate CRS*.

STORAGE

Protected from light.

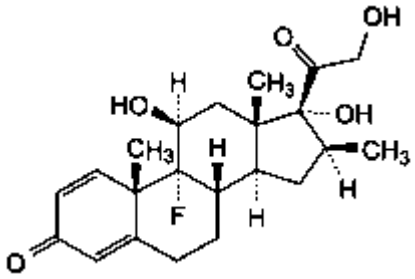
IMPURITIES

Specified impurities *B, C, D, E, G, H, I.*

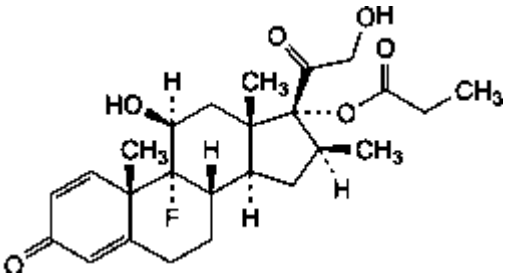
www.webofpharma.com

https://thuvienthuocngocanh.com/

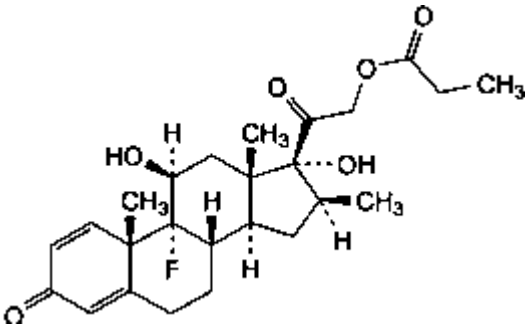
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, F.



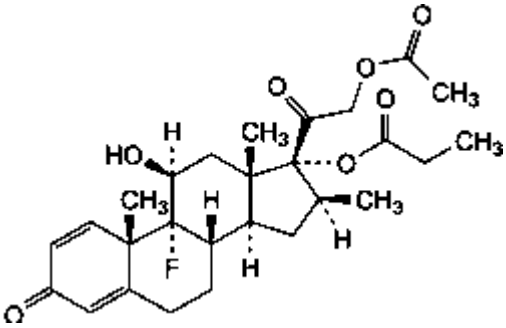
A. 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (betamethasone),



B. 9-fluoro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (betamethasone 17-propionate),



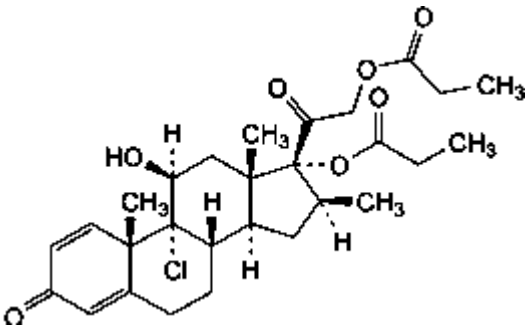
C. 9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl propanoate (betamethasone 21-propionate),



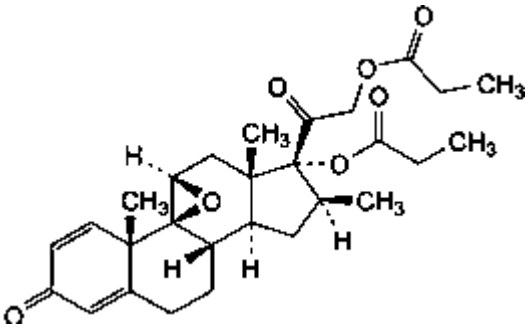
D. 9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl 21-acetate 17-propanoate (betamethasone 21-acetate 17-propionate),

www.webofpharma.com

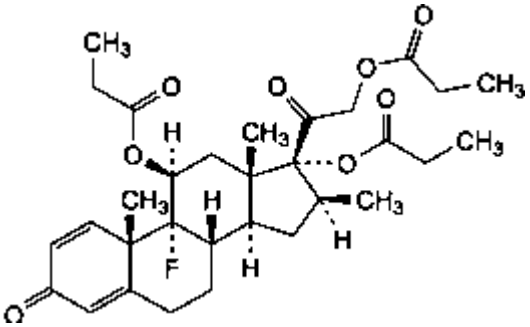
https://thuocngocanh.com/



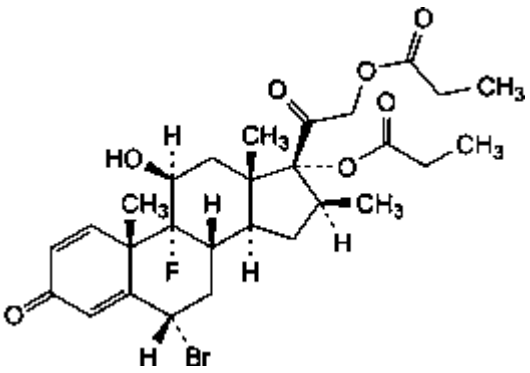
E. 9-chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate (beclometasone dipropionate),



F. 9,11β-epoxy-16β-methyl-3,20-dioxo-9β-pregna-1,4-diene-17,21-diyl dipropanoate (9β,11β-epoxybetamethasone dipropionate),



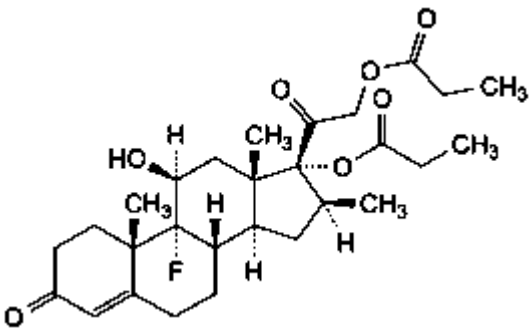
G. 9-fluoro-16β-methyl-3,20-dioxopregna-1,4-diene-11β,17,21-triyl tripropanoate (betamethasone tripropionate),



H. 6α-bromo-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate (6α-bromobetamethasone dipropionate),

www.webofpharma.com

https://thuocngocanh.com/



I. 9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregn-4-ene-17,21-diyl dipropanoate (1,2-dihydrobetamethasone dipropionate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Eye Drops

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone Eye Drops are a sterile solution of Betamethasone Sodium Phosphate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of betamethasone sodium phosphate, $C_{22}H_{28}FNa_2O_8P$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the eye drops, diluted if necessary with *water*, to contain 0.1% w/v of Betamethasone Sodium Phosphate.

(2) 0.1% w/v of *betamethasone sodium phosphate BPCRS*.

(3) A mixture of equal volumes of solutions (1) and (2).

(4) A mixture of equal volumes of solution (2) and a 0.1% w/v solution of *prednisolone sodium phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, heat at 110° for 10 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *acetic anhydride*, 20 volumes of *water* and 60 volumes of *butan-1-ol*, prepared immediately before use.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two principal spots with almost identical Rf values.

CONFIRMATION

The chromatograms obtained with solutions (1), (2) and (3) show single principal spots with similar Rf values.

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to betamethasone sodium phosphate in the chromatogram obtained with solution (1).

C. To a volume containing 0.2 mg of Betamethasone Sodium Phosphate, add slowly 1 mL of *sulfuric acid* and allow to stand for 2 minutes. A brownish yellow colour but no red colour or yellowish green fluorescence is produced.

TESTS

Acidity or alkalinity

pH, 7.0 to 8.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light and using the following solutions in the mobile phase.

(1) Dilute the eye drops if necessary to give a solution containing 0.10% w/v of Betamethasone Sodium Phosphate.

(2) Dilute 1 volume of solution (1) to 50 volumes with *water*.

(3) 0.0060% w/v each of *betamethasone sodium phosphate BPCRS* and *betamethasone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 241 nm.

(f) Inject 20 µL of each solution.

(g) For solutions (1) and (2) record the chromatogram for three times the retention time of the principal peak.

MOBILE PHASE

40 volumes of *methanol* and 60 volumes of *citro-phosphate buffer pH 5.0*.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3) the *resolution factor* between the peaks due to betamethasone sodium phosphate and betamethasone is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to betamethasone is not greater than 1.3 times the area of the principal peak in the chromatogram obtained with solution (2) (2.6%);

the area of any other *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak the area of which is less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the eye drops containing 5 mg of Betamethasone Sodium Phosphate with 10 mL of *methanol* and dilute to 25 mL with *water*.

(2) A mixture of 5 mL of a 0.1% w/v solution of *betamethasone sodium phosphate BPCRS* in *water* (solution A) and 10 mL of a 0.06% w/v solution of *hydrocortisone* (internal standard) in *methanol* and sufficient *water* to produce 25 mL.

(3) Prepare in the same manner as solution (1) but using 10 mL of the internal standard solution in place of the methanol.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 241 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of *methanol* and 55 volumes of *citro-phosphate buffer pH 5.0*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{28}FNa_2O_8P$ in solution A by measuring the *absorbance*, Appendix II B, of an aliquot diluted with *water* to contain 0.002% w/v of Betamethasone Sodium Phosphate at the maximum at 241 nm and taking 297 as the value of A(1%, 1 cm) at the maximum at 241 nm. Calculate the content of $C_{22}H_{28}FNa_2O_8P$ in the eye drops using peak areas.

STORAGE

Betamethasone Eye Drops should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Injection

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone Injection is a sterile solution of Betamethasone Sodium Phosphate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. To a volume of the injection containing the equivalent of 4 mg of betamethasone add 1 mL of *water* and sufficient *absolute ethanol* to produce 40 mL. Place 2 mL of the solution in a stoppered tube, add 10 mL of *phenylhydrazine-sulfuric acid solution*, mix, warm in a water bath at 60° for 20 minutes and cool immediately. The *absorbance* of the resulting solution at the maximum at 450 nm is not more than 0.1, Appendix II B.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the injection, if necessary, with sufficient *water* to produce a solution containing the equivalent of 2 mg of betamethasone per mL.

(2) 0.25% w/v solution of *betamethasone sodium phosphate BPCRS* in *water*.

(3) A mixture of equal volumes of solutions (1) and (2).

(4) A mixture of equal volumes of solution (1) and a 0.25% w/v solution of *prednisolone sodium phosphate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below and prepare immediately before use.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, heat at 110° for 10 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *acetic anhydride*, 20 volumes of *water* and 60 volumes of *butan-1-ol*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The chromatograms obtained with solutions (1), (2) and (3) show single spots with similar Rf values;

the chromatogram obtained with solution (4) shows two principal spots with almost identical Rf values.

Secondary spots due to excipients may also be observed in the chromatograms obtained with solutions (1), (3) and (4).

C. Evaporate a volume containing the equivalent of 2 mg of betamethasone to dryness on a water bath, dissolve the residue in 2 mL of *sulfuric acid* and allow to stand for 2 minutes. No red colour is produced.

TESTS

Alkalinity

pH, 8.0 to 9.0, Appendix V L.

Colour

The injection, diluted if necessary with *water* to contain the equivalent of 2 mg of betamethasone per mL, is not more intensely coloured than *reference solution* BY_4, Appendix IV B, Method I.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) Dilute the injection with mobile phase, if necessary, to give a solution containing the equivalent of 0.10% w/v of betamethasone.
(2) Dilute 1 volume of solution (1) to 50 volumes with mobile phase.
(3) 0.0060% w/v each of *betamethasone sodium phosphate BPCRS* and *betamethasone* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 241 nm.
(f) Inject 20 µL of each solution. For solutions (1) and (2) record the chromatogram for three times the retention time of the principal peak.

MOBILE PHASE

40 volumes of methanol and 60 volumes of citro-phosphate buffer pH 5.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to betamethasone sodium phosphate and betamethasone is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thietbiuocngocanh.com/

the area of any peak corresponding to betamethasone is not greater than 1.3 times the area of the principal peak in the chromatogram obtained with solution (2)(2.6%);

the area of any other *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2)(3%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2)(5%).

Disregard any peak the area of which is less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Dilute a volume of the injection containing the equivalent of 8 mg of betamethasone to 50 mL with *methanol (50%)*.

(2) Dilute 5 mL of a 0.045% w/v solution of *betamethasone sodium phosphate BPCRS* in *water* (solution A) to 10 mL with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 241 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of methanol and 55 volumes of citro-phosphate buffer pH 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the injection, determining the exact strength of $C_{22}H_{29}FO_5$ in solution (2) as follows. Dilute 3 mL of solution A to 50 mL with *water* and measure the *absorbance*, Appendix II B, of the resulting solution at the maximum at 241 nm, taking 391 as the value of A(1%, 1 cm) for betamethasone.

STORAGE

Betamethasone Injection should be stored at a temperature not exceeding 30° and protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of betamethasone in a suitable dose-volume.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

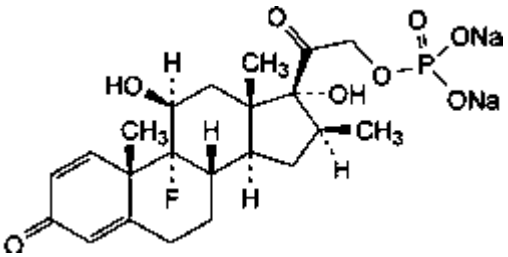
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Sodium Phosphate

General Notices

(Ph. Eur. monograph 0810)



$C_{22}H_{28}FNa_2O_8P$ 516.4 *151-73-5*

Action and use

Glucocorticoid.

Preparations

Betamethasone Eye Drops

Betamethasone Injection

Betamethasone Sodium Phosphate Tablets

Ph Eur

DEFINITION

Disodium 9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl phosphate.

Content

96.0 per cent to 103.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *betamethasone sodium phosphate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol (96 per cent) R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 10 mg of *betamethasone sodium phosphate CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat the plate at 90 °C for 35 min or until the spots appear and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, an intense reddish-brown colour develops. Add the solution to 10 mL of *water R* and mix. The colour disappears and a clear solution remains.

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

https://thuocngocanh.com/

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

pH (*2.2.3*)

7.5 to 9.0.

Dilute 1 mL of solution S to 5 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

+ 98 to + 104 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 62.5 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 25 mg of *betamethasone sodium phosphate CRS* and 25 mg of *dexamethasone sodium phosphate CRS* in the mobile phase and dilute to 25 mL with the mobile phase. Dilute 1 mL of this solution to 25 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase In a 250 mL conical flask, weigh 1.360 g of *potassium dihydrogen phosphate R* and 0.600 g of *hexylamine R*, mix and allow to stand for 10 min and then dissolve in 185 mL of *water for chromatography R*; add 65 mL of *acetonitrile R*, mix and filter (0.45 µm).

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Equilibration With the mobile phase for about 45 min.

Injection 20 µL.

Run time Twice the retention time of betamethasone sodium phosphate.

Retention time Betamethasone sodium phosphate = about 14 min; dexamethasone sodium phosphate = about 15.5 min.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to betamethasone sodium phosphate and dexamethasone sodium phosphate; if necessary, increase the concentration of *acetonitrile R* or increase the concentration of *water for chromatography R* in the mobile

www.webofpharma.com

https://thuocngocanh.com/

phase.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent), and not more than 1 such peak has an area greater than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3 per cent);

— *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Inorganic phosphate

Maximum 1 per cent.

Dissolve 50 mg in *water R* and dilute to 100 mL with the same solvent. To 10 mL of the solution add 5 mL of *molybdovanadic reagent R*, mix and allow to stand for 5 min. Any yellow colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 mL of *phosphate standard solution (5 ppm PO_4) R*.

Water (*2.5.12*)

Maximum 8.0 per cent, determined on 0.200 g.

ASSAY

Dissolve 0.100 g in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 250.0 mL with *water R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 241 nm.

Calculate the content of $C_{22}H_{28}FNa_2O_8P$ taking the specific absorbance to be 297.

STORAGE

In an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Sodium Phosphate Tablets

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone Sodium Phosphate Tablets contain Betamethasone Sodium Phosphate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the powdered tablets containing the equivalent of 2 mg of betamethasone in 25 mL of *water*, add 2.5 g of *sodium chloride* and 1 mL of *hydrochloric acid*, extract with 25 mL of *chloroform* and discard the chloroform layer. Extract with 25 mL of *tributyl orthophosphate* and discard the aqueous layer.

(2) Prepare in the same manner as solution (1) but using 2.5 mg of *betamethasone sodium phosphate BPCRS* in place of the powdered tablets.

(3) Mix equal volumes of solutions (1) and (2).

(4) Mix equal volumes of solution (1) and a solution prepared in the same manner as solution (1) but using 2.5 mg of *prednisolone sodium phosphate BPCRS* in place of the powdered tablets.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below prepared immediately before use.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, heat at 110° for 10 minutes, spray the hot plate with *ethanolic sulfuric acid (20%)* and again heat at 110° for 10 minutes.

MOBILE PHASE

20 volumes of *acetic anhydride*, 20 volumes of *water* and 60 volumes of *butan-1-ol* prepared immediately before use.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless the chromatogram obtained with solution (4) shows two principal spots with almost identical Rf values.

CONFIRMATION

The chromatograms obtained with solutions (1), (2) and (3) show single spots with identical Rf values.

B. Mix a quantity of the powdered tablets containing the equivalent of 0.4 mg of betamethasone with 1 mL of *sulfuric acid* and allow to stand for 5 minutes. A pale yellow colour is produced (distinction from prednisolone sodium phosphate tablets).

TESTS

Disintegration

Maximum time, 5 minutes, Appendix XII A1.

Uniformity of content

Tablets containing less than the equivalent of 2 mg and/or less than 2% w/w of betamethasone comply with the requirements stated under Tablets using the following method of analysis. Carry out the procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve one tablet as completely as possible in 5 mL of *water*, add 5 mL of *methanol* and filter.Add sufficient *methanol (50%)* to produce a solution expected to contain 0.00325% w/v of betamethasone sodium phosphate.
(2) 0.0065% w/v of *betamethasone sodium phosphate BPCRS* in *water*. Dilute 1 volume of this solution to 2 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 241 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of *methanol* and 55 volumes of *citro-phosphate buffer pH 5.0*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in each tablet, determining the exact strength of the solution of *betamethasone sodium phosphate BPCRS* as described in the Assay.

ASSAY

Weigh and powder 20 tablets. Carry out the procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of the powdered tablets containing 2.5 mg of betamethasone for 20 minutes with 25 mL of *water*, dilute to 50 mL with *methanol*, mix and filter through a glass fibre filter (Whatman GF/C is suitable).

(2) Dilute 5 mL of a 0.014% w/v solution of *betamethasone sodium phosphate BPCRS* in *water* (solution A) to 10 mL with *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the tablets, determining the exact strength of $C_{22}H_{29}FO_5$ in solution (2) as follows. Dilute 5 mL of solution A to 25 mL with *water* and measure the *absorbance*, Appendix II B, of the resulting solution at the maximum at 241 nm, taking 391 as the value of A(1%, 1 cm) for betamethasone.

STORAGE

Betamethasone Sodium Phosphate Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of betamethasone.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Tablets

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone Tablets contain Betamethasone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 25 mg of Betamethasone with 150 mL of *dichloromethane* for 30 minutes, filter, wash the filtrate with 20 mL of *water*, dry over *anhydrous sodium sulfate*, evaporate the solution to dryness and dry the residue at 105° for 2 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of betamethasone *(RS 029)*.

B. The residue obtained in test A complies with the test for the *identification of steroids*, Appendix III A, using *impregnating solvent I* and *mobile phase A*. At a fourth point apply to the plate 2 µL of a mixture of equal volumes of solution (1) and a 0.25% w/v solution of *dexamethasone BPCRS* in a mixture of 9 volumes of *chloroform* and 1 volume of *methanol*. The chromatogram obtained with this solution shows two principal spots with almost identical Rf values.

C. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to betamethasone in the chromatogram obtained with solution (2).

TESTS

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Betamethasone comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Finely crush one tablet, add 20 mL of a 0.002% w/v solution of *hydrocortisone* in *methanol (50%)*, shake for 10 minutes and filter through a glass-fibre filter paper (Whatman GF/C is suitable).

(2) 0.0025% w/v of *betamethasone BPCRS* and 0.002% w/v of *hydrocortisone* (internal standard) in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.4 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

47 volumes of *methanol* and 53 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in each tablet using the ratios of the peak areas and the declared content of $C_{22}H_{29}FO_5$ in *betamethasone BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Betamethasone

Use the average of the individual results determined in the test for Uniformity of content.

For Tablets containing 2 mg or more and 2% w/w or more of Betamethasone

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powder containing 2.5 mg of Betamethasone add 20 mL of *methanol (50%)*, shake for 10 minutes and filter through a glass-fibre filter paper (Whatman GF/C is suitable).

(2) 0.0125% w/v of *betamethasone BPCRS* and 0.010% w/v of *hydrocortisone* (internal standard) in *methanol (50%)*.

(3) Prepare the solution in the same manner as solution (1) but use 20 mL of a 0.01% w/v solution of *hydrocortisone* in *methanol (50%)* in place of the 20 mL of *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the tablets using the ratios of the peak areas and the declared content of $C_{22}H_{29}FO_5$ in *betamethasone BPCRS*.

STORAGE

Betamethasone Tablets should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

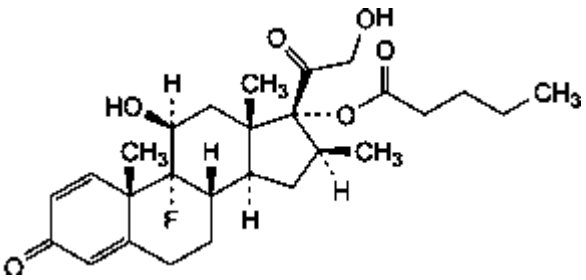
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Valerate

General Notices

(Ph. Eur. monograph 0811)



$C_{27}H_{37}FO_6$ 476.6 *2152-44-5*

Action and use

Glucocorticoid.

Preparations

Betamethasone and Clioquinol Cream

Betamethasone and Clioquinol Ointment

Betamethasone Valerate and Coal Tar Paste

Betamethasone Valerate Cream

Betamethasone Valerate Lotion

Betamethasone Valerate Ointment

Betamethasone Valerate Scalp Application

Ph Eur

DEFINITION

9-Fluoro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl pentanoate.

Content

97.0 per cent to 103.0 per cent (dried substance).

www.webofpharma.com

https://thuocngocanh.com/

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in methylene chloride, soluble in ethanol (96 per cent).

mp

About 192 °C, with decomposition.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *betamethasone 17-valerate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methylene chloride R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Examine the chromatograms obtained in the test for related substances.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Specific optical rotation (*2.2.7*)

+ 77 to + 83 (dried substance).

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light. Prepare the solutions immediately before use.*

Solvent mixture *glacial acetic acid R*, mobile phase (1:1000 *V/V*).

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 12.5 mg of *betamethasone valerate for system suitability CRS* (containing impurities D and G) in 5.0 mL of the solvent mixture. Use 1.0 mL of this solution to dissolve the contents of a vial of *betamethasone valerate impurity mixture CRS* (containing impurities C, H and I).

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Dissolve 6 mg of *betamethasone CRS* (impurity A) and 3 mg of *betamethasone 21-valerate CRS* (impurity E) in 30.0 mL of the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 20 °C.

Mobile phase *acetonitrile R*, *water R* (50:50 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 239 nm.

Injection 20 µL.

Run time 2.5 times the retention time of betamethasone valerate.

Identification of impurities Use the chromatogram supplied with *betamethasone valerate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C, D, G, H and I; use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and E.

Relative retention With reference to betamethasone valerate (retention time = about 20 min): impurity A = about 0.3; impurity I = about 0.6; impurity C = about 0.8; impurity H = about 1.3; impurity D = about 1.4; impurity E = about 1.6; impurity G = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 1.7 between the peaks due to impurities H and D.

Limits:

— *impurity A*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *impurities E, G*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities C, H, I*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of this solution to 50.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 240 nm.

Calculate the content of $C_{27}H_{37}FO_6$ taking the specific absorbance to be 325.

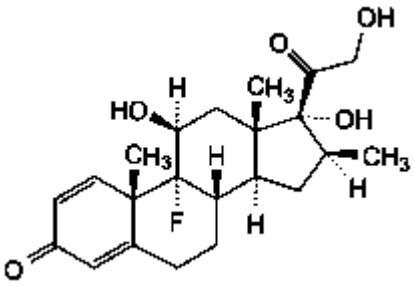
STORAGE

Protected from light.

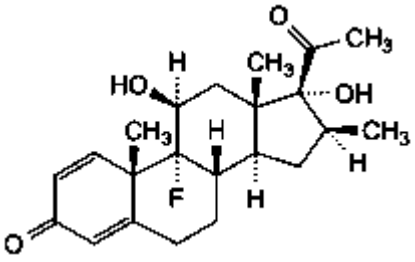
IMPURITIES

Specified impurities *A, C, E, G, H, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, F.*



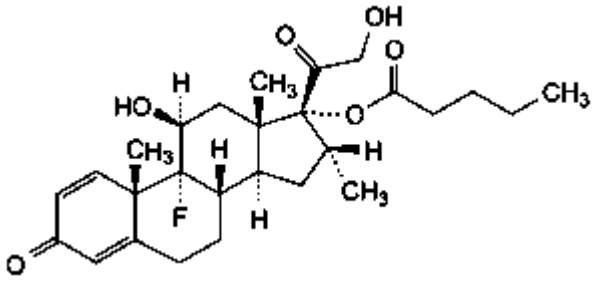
A. 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (betamethasone),



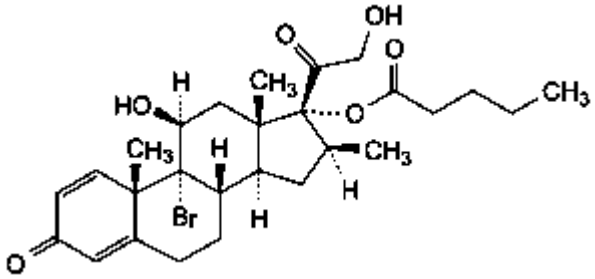
B. 9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione (21-deoxy-betamethasone),

www.webofpharma.com

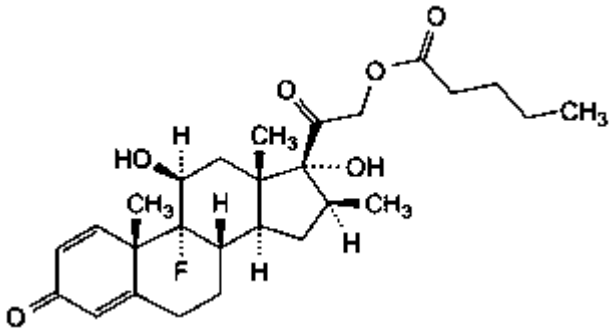
https://thuocngocanh.com/



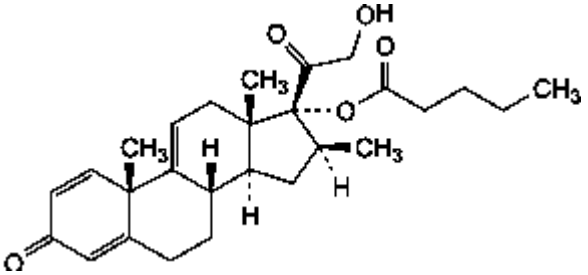
C. 9-fluoro-11β,21-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl pentanoate (dexamethasone 17-valerate),



D. 9-bromo-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl pentanoate (9-bromo-betamethasone valerate),



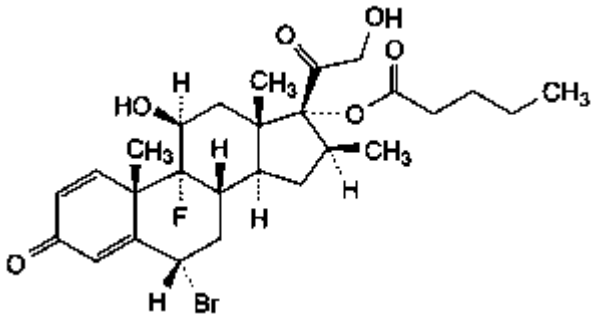
E. 9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl pentanoate (betamethasone 21-valerate),



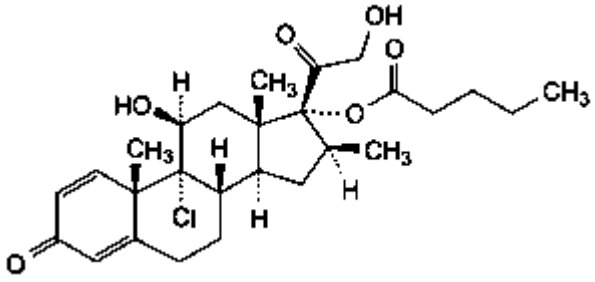
F. 21-hydroxy-16β-methyl-3,20-dioxopregna-1,4,9(11)-trien-17-yl pentanoate (betamethasone valerate δ-9(11)),

www.webofpharma.com

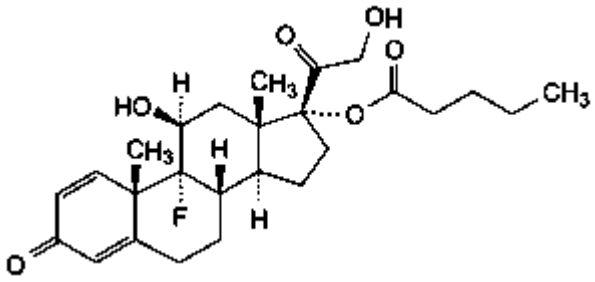
https://thuocngocanh.com/



G. 6α-bromo-9-fluoro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl pentanoate (6α-bromo-betamethasone valerate),



H. 9-chloro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl pentanoate (beclomethasone 17-valerate),



I. 9-fluoro-11β,21-dihydroxy-3,20-dioxopregna-1,4-dien-17-yl pentanoate (9-fluoro-prednisolone 17-valerate).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Valerate and Coal Tar Paste

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used in the treatment of psoriasis.

DEFINITION

Betamethasone Valerate and Coal Tar Paste contains Betamethasone Valerate and Coal Tar in a suitable basis containing Zinc Oxide.

The paste complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the paste also complies with the requirements stated under Unlicensed Medicines.

Content of betamethasone valerate, $C_{27}H_{37}FO_6$

90.0 to 110.0% of the stated amount.

Content of zinc oxide, ZnO

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the paste containing 20 µg of Betamethasone Valerate in 10 mL of *chloroform* and filter (Whatman No. 1 paper is suitable). Evaporate the *chloroform* to dryness and extract the residue with 1 mL of a mixture of 30 volumes of *methanol* and 70 volumes of *water*.

(2) 20 µg of *betamethasone valerate BPCRS* in a mixture of 30 volumes of *methanol* and 70 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*. Heat the plate at 105° for 5 minutes and spray while warm with a mixture containing 1 volume of a 0.2% w/v solution of *alkaline tetrazolium blue* in *methanol* and 9 volumes of 10% w/v *methanolic sodium hydroxide*.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

Mix 1 volume of *ethyl acetate*, 1 volume of *water* and 2 volumes of *1,2 –dichloroethane*. Use the lower layer.

CONFIRMATION

By each method of visualisation, the principal spot in the chromatogram obtained with solution (1) corresponds in position and intensity to that in the chromatogram obtained with solution (2).

B. In the Assay for betamethasone valerate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. Heat 0.5 g of the paste gently in a porcelain dish over a small flame until the basis is completely volatilised or charred. Increase the heat until all the carbon is removed. The residue obtained is yellow when hot and white when cool.

ASSAY

For betamethasone valerate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.1% w/v of *beclometasone dipropionate BPCRS* (internal standard) in *methanol*.

(2) To a quantity of the paste containing 0.25 mg of Betamethasone Valerate add 1 mL of solution (1) and 10 mL of *chloroform*. Mix using a vortex mixer and filter (Whatman No. 1 filter paper is suitable), rinsing with a further 10 mL of *chloroform*. Evaporate the filtrate in a water bath at 40° to 50° in a current of air. Dissolve the residue in 25 mL of *hexane* and transfer to a separating funnel containing 20 mL of *ethanolic hydrochloric acid*, washing the flask with *hexane*. Repeat the extraction with two 10-mL quantities of *ethanolic hydrochloric acid*, filtering the extracts through absorbent cotton, and add sufficient *ethanolic hydrochloric acid* to produce 50 mL.

(3) 0.05% w/v of *betamethasone valerate BPCRS* in *methanol*.

(4) Dilute 1 volume of solution (1) and 1 volume of solution (3) to 50 volumes with *ethanolic hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of solutions (2), (3) and (4).

MOBILE PHASE

4 volumes of *water* and 6 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions, the retention time for betamethasone valerate is about 8 minutes and the retention time for beclometasone dipropionate is about 14 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the two principal peaks is at least 1.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{27}H_{37}FO_6$ in the paste using the declared content of $C_{27}H_{37}FO_6$ in *betamethasone valerate BPCRS*.

For zinc oxide

Heat 0.5 g of the paste gently in a porcelain dish over a small flame until the basis is completely volatilised or charred. Increase the heat until all the carbon is removed. Dissolve the residue in 10 mL of 2M *acetic acid* and add sufficient *water* to produce 50 mL. To the resulting solution add 50 mg of *xylenol orange triturate* and sufficient *hexamine* to produce a violet-pink colour. Add a further 2 g of *hexamine* and titrate with 0.1M *disodium edetate VS* until the solution becomes yellow. Each mL of 0.1M *disodium edetate VS* is equivalent to 8.138 mg of ZnO.

STORAGE

Betamethasone Valerate and Coal Tar Paste should be stored at a temperature of 2° to 8°.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Valerate Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone Valerate Cream contains Betamethasone Valerate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the cream containing the equivalent of 0.5 mg of betamethasone in 20 mL of *methanol (80%)* by heating on a water bath until the methanol begins to boil. Shake vigorously, cool in ice for 30 minutes and centrifuge. Mix 10 mL of the supernatant liquid with 3 mL of *water* and 5 mL of *chloroform*, shake vigorously, allow the layers to separate and evaporate the chloroform layer to dryness in a current of nitrogen with gentle heating. Dissolve the residue in 1 mL of *chloroform*.

(2) 0.03% w/v of *betamethasone valerate BPCRS* in *chloroform*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air until the solvent has evaporated, heat at 105° for 5 minutes and spray while hot with *alkaline tetrazolium blue solution*.

MOBILE PHASE

5 volumes of *absolute ethanol*, 10 volumes of *acetone* and 100 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2). The spot in the chromatogram obtained with solution (3) appears as a single compact spot.

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to betamethasone valerate in the chromatogram obtained with solution (3).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the cream containing the equivalent of 2 mg of betamethasone with 100 mL of hot *hexane* for 2 minutes, cool, extract the mixture with 20 mL of *ethanol (96%)* and filter the lower, ethanolic layer through absorbent cotton previously washed with *ethanol (75%)*. Repeat the extraction of the hexane mixture with two 10-mL quantities of *ethanol (75%)*, filtering each extract in turn through the absorbent cotton. Combine the filtrates, add 5 mL of a 0.072% w/v solution of *beclometasone dipropionate BPCRS* (internal standard) and dilute to 50 mL with *ethanol (75%)*.

(2) Shake a quantity of the cream containing the equivalent of 2 mg of betamethasone with 100 mL of hot *hexane* for 2 minutes, cool, extract the mixture with 20 mL of *ethanol (96%)* and filter the lower, ethanolic layer through absorbent cotton previously washed with *ethanol (75%)*. Repeat the extraction of the hexane mixture with two 10-mL quantities of *ethanol (75%)*, filtering each extract in turn through the absorbent cotton and dilute the combined filtrates to 50 mL with *ethanol (75%)*.

(3) Mix 10 mL of a solution containing 0.024% w/v of *betamethasone valerate BPCRS* and 0.0012% w/v of *betamethasone 21-valerate BPCRS* in *ethanol (80%)* with 5 mL of a 0.072% w/v solution of *beclometasone dipropionate BPCRS* (internal standard) in *ethanol (80%)* and dilute to 50 mL with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

42 volumes of *absolute ethanol* and 58 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to betamethasone valerate (retention time about 5 minutes) and betamethasone 21-valerate (retention time about 7 minutes) is greater than 1.0. If necessary, adjust the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the cream using the declared content of $C_{22}H_{29}FO_5$, in *betamethasone valerate BPCRS*.

STORAGE

Betamethasone Valerate Cream should be protected from light.

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of betamethasone.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Valerate Lotion

General Notices

Betamethasone Valerate Cutaneous Solution

Action and use

Glucocorticoid.

DEFINITION

Betamethasone Valerate Lotion is a *cutaneous solution*. It contains Betamethasone Valerate in a suitable vehicle.

The lotion complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the preparation being examined containing the equivalent of 1 mg of betamethasone with 5 mL of *methanol (80%)* by heating on a water bath until the methanol begins to boil. Shake vigorously, cool in ice and filter. Transfer the filtrate to a separating funnel and add 0.5 mL of *water* and 1 mL of *chloroform*. Shake vigorously, allow the layers to separate and use the chloroform layer.

(2) 0.05% w/v of *betamethasone valerate BPCRS* in *chloroform*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air until the solvent has evaporated, heat at 105° for 5 minutes and spray while hot with *alkaline tetrazolium blue solution*.

MOBILE PHASE

5 volumes of *absolute ethanol*, 10 volumes of *acetone* and 100 volumes of *chloroform*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2). The spot in the chromatogram obtained with solution (3) appears as a single compact spot.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to betamethasone valerate in the chromatogram obtained with solution (3).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the lotion containing the equivalent of 3 mg of betamethasone in a mixture of 10 mL of *ethanol (65%)* and 50 mL of *hexane*, shake for 2 minutes and filter the lower, ethanolic layer through absorbent cotton previously washed with *ethanol (65%)*. Repeat the extraction of the hexane mixture with two 5-mL quantities of *ethanol (65%)*, filtering the ethanol extracts through the absorbent cotton, add 5 mL of a 0.11% w/v solution of *beclometasone dipropionate BPCRS* (internal standard)to the combined filtrates and mix.
(2) Disperse a quantity of the lotion containing the equivalent of 3 mg of betamethasone in a mixture of 10 mL of *ethanol (65%)* and 50 mL of *hexane*, shake for 2 minutes and filter the lower, ethanolic layer through absorbent cotton previously washed with *ethanol (65%)*. Repeat the extraction of the hexane mixture with two 5-mL quantities of *ethanol (65%)*, filtering the ethanol extracts through the absorbent cotton, add 5 mL of *ethanol (65%)* to the combined filtrates and mix.
(3) Mix 20 mL of a solution containing 0.018% w/v of *betamethasone valerate BPCRS* and 0.0010% w/v of *betamethasone 21-valerate BPCRS* in *ethanol (65%)* with 5 mL of a 0.11% w/v solution of *beclometasone dipropionate BPCRS* (internal standard) in *ethanol (65%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 238 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

42 volumes of *absolute ethanol* and 58 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to betamethasone valerate (retention time about 5 minutes) and betamethasone 21-valerate (retention time about 7 minutes) is greater than 1.0. If necessary, adjust the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the lotion using the declared content of $C_{22}H_{29}FO_5$, in *betamethasone valerate BPCRS*.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Betamethasone Valerate Lotion should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of betamethasone.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Valerate Ointment

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone Valerate Ointment contains Betamethasone Valerate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Complies with test A for Identification described under Betamethasone Valerate Lotion preparing solution (1) in the following manner. Disperse a quantity of the ointment containing the equivalent of 1 mg of betamethasone in 10 mL of *methanol* by heating on a water bath until the methanol begins to boil, shake vigorously, cool in ice for 30 minutes and filter. Evaporate the filtrate to dryness in a current of nitrogen with gentle heating and dissolve the residue in 0.5 mL of *chloroform*. Solution (2) contains 0.24% w/v of *betamethasone valerate BPCRS* in *chloroform*.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to betamethasone valerate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) mix 10 mL of a solution containing 0.024% w/v of *betamethasone valerate BPCRS* and 0.0012% w/v of *betamethasone 21-valerate BPCRS* in *ethanol (65%)* with 5 mL of a 0.072% w/v solution of *beclometasone dipropionate BPCRS* (internal standard) in *ethanol (65%)* and dilute to 50 mL with *ethanol (65%)*. For solution (2) disperse a quantity of the ointment containing the equivalent of 2 mg of betamethasone in 100 mL of hot *hexane*, cool, extract with 20 mL of *ethanol (65%)* and filter the lower, ethanolic layer through absorbent cotton previously washed with *ethanol (65%)*; repeat the extraction of the hexane mixture with two 10-mL quantities of *ethanol (65%)*, filtering each extract in turn through the absorbent cotton and dilute the combined filtrates to 50 mL with *ethanol (65%)*. Prepare solution (3) in the same manner as solution (2) but add 5 mL of the 0.072% w/v solution of the internal standard in *ethanol (65%)* before diluting to 50 mL.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable) and maintained at 60°, (b) as the mobile phase with a flow rate of 2 mL per minute a mixture of *absolute ethanol* and *water* adjusted so that the *resolution factor* between the peaks due to betamethasone valerate

www.webofpharma.com

https://thuocngocanh.com/

(retention time about 5 minutes) and betamethasone 21 valerate (retention time about 7 minutes) is more than 1.0 (a mixture of 42 volumes of *absolute ethanol* and 58 volumes of *water* is usually suitable) and (c) a detection wavelength of 238 nm.

Calculate the content of $C_{22}H_{29}FO_5$ in the ointment using the declared content of $C_{22}H_{29}FO_5$ in *betamethasone valerate BPCRS*.

STORAGE

Betamethasone Valerate Ointment should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of betamethasone.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betamethasone Valerate Scalp Application

General Notices

Action and use

Glucocorticoid.

DEFINITION

Betamethasone Valerate Scalp Application is a *cutaneous solution*. It contains Betamethasone Valerate in a suitable liquid basis.

The application complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of betamethasone, $C_{22}H_{29}FO_5$

90.0 to 115.0% of the stated amount.

IDENTIFICATION

A. Complies with test A for Identification described under Betamethasone Valerate Lotion, preparing solution (1) by diluting a suitable volume of the application with *absolute ethanol* to give a solution containing the equivalent of 0.04% w/v of betamethasone.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to betamethasone valerate in the chromatogram obtained with solution (1).

ASSAY

Carry out the Assay described under Betamethasone Valerate Lotion, preparing solutions (2) and (3) in the following manner. For solution (2) dilute a quantity of the application containing the equivalent of 3 mg of betamethasone to 25 mL with *ethanol (65%)*. For solution (3) add 5 mL of a 0.11% w/v solution of the internal standard to a quantity of the application containing the equivalent of 3 mg of betamethasone and dilute to 25 mL with *ethanol (65%)*.

STORAGE

Betamethasone Valerate Scalp Application should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of betamethasone.

The label indicates the pharmaceutical form as ‘cutaneous solution’.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betaxolol Eye Drops, Solution

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Betaxolol Eye Drops, Solution are a sterile solution of Betaxolol Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of betaxolol, $C_{18}H_{29}NO_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the eye drops with *water* to produce a solution containing the equivalent of 0.1% w/v of betaxolol. Shake 1 mL of the solution with 4 mL of *water*, 0.1 mL of 13.5M *ammonia* and 2 mL of *chloroform*, centrifuge and use the chloroform layer.

(2) Prepare solution (2) in the same manner as solution (1) but using a 0.1% w/v solution of *betaxolol hydrochloride BPCRS* in place of the eye drops.

(3) A mixture of equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a solution prepared by dissolving 5 g of *iodine* and 10 g of *potassium iodide* in sufficient *water* to produce 100 mL and mixing 20 mL of the resulting solution with 30 mL of *water* and 50 mL of 2M *acetic acid*. Examine the plate immediately; spots due to betaxolol appear brown.

MOBILE PHASE

30 volumes of a solution prepared by diluting 1 volume of 13.5M *ammonia* to 50 volumes with *propan-2-ol* immediately before use and 70 volumes of *chloroform*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single, compact spot.

www.webofpharma.com

https://thuocngocanh.com/

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 7.8, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a suitable volume of the eye drops to produce a solution containing the equivalent of 0.02% w/v of betaxolol.
(2) Dilute 1 volume of solution (1) to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS-2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 3 g of *sodium dodecyl sulfate* in 450 mL of the following solution. 45 volumes of a buffer solution prepared as described below and 55 volumes of *acetonitrile*. To prepare the buffer solution add 5 mL of *orthophosphoric acid* to 990 mL of *water*, adjust the pH to 3.0 with 2M *ammonia* and add sufficient *water* to produce 1000 mL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency*, determined on the peak due to betaxolol is at least 8000 *theoretical plates* per metre and the *symmetry factor* of the principal peak is not more than 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of not more than one *secondary peak* is greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute the eye drops to produce a solution containing the equivalent of 0.01% w/v of betaxolol.

(2) 0.012% w/v of *betaxolol hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS-2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of *water* containing 0.71% w/v of *anhydrous disodium hydrogen orthophosphate* and 0.91% w/v of *dimethylamine hydrochloride*, adjusted to pH 3.0 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{29}NO_3$ in the eye drops using the declared content of $C_{18}H_{29}NO_3$ in *betaxolol hydrochloride BPCRS*.

STORAGE

Betaxolol Eye Drops, Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of betaxolol.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betaxolol Eye Drops, Suspension

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Betaxolol Eye Drops, Suspension are a sterile suspension of Betaxolol Hydrochloride in Purified Water containing suitable binding and suspending agents.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of betaxolol, $C_{18}H_{29}NO_3$

90.0 to 110.0% of the stated amount.

The eye drops should be shaken vigorously before carrying out the following tests.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the eye drops with *water* to produce a solution containing the equivalent of 0.1% w/v of betaxolol. Shake 1 mL of the solution with 4 mL of *water*, 0.1 mL of 13.5M *ammonia* and 2 mL of *chloroform*, centrifuge and use the chloroform layer.

(2) Prepare solution (2) in the same manner as solution (1) but using a 0.1% w/v solution of *betaxolol hydrochloride BPCRS* in place of the eye drops.

(3) Equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a solution prepared by dissolving 5 g of *iodine* and 10 g of *potassium iodide* in sufficient *water* to produce 100 mL and mixing 20 mL of the resulting solution with 30 mL of *water* and 50 mL of 2M *acetic acid*. Examine the plate immediately; spots due to betaxolol appear brown.

MOBILE PHASE

30 volumes of a solution prepared by diluting 1 volume of 13.5M *ammonia* to 50 volumes with *propan-2-ol* immediately before use and 70 volumes of *chloroform*.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single, compact spot.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Particle size

Examine using an automated light obscuration instrument such as that described in Appendix XIII A. Not less than 99.5% of the particles are less than 25 µm, not less than 99.95% are less than 50 µm and none exceeds 75 µm.

Acidity or alkalinity

pH, 6.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a suitable volume of the eye drops with sufficient of the mobile phase to produce a solution containing the equivalent of 0.02% w/v of betaxolol, centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS-2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 3 g of *sodium dodecyl sulfate* in 450 mL of the following solution. 45 volumes of a buffer solution prepared as described below and 55 volumes of *acetonitrile*. To prepare the buffer solution add 5 mL of *orthophosphoric acid* to 990 mL of *water*, adjust the pH to 3.0 with 2M *ammonia* and add sufficient *water* to produce 1000 mL.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency*, determined on the peak due to betaxolol is at least 8000 *theoretical plates* per metre and the *symmetry factor* of the principal peak is not more than 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of not more than one *secondary peak* is greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

Bound betaxolol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the eye drops with sufficient of the mobile phase to produce a solution containing the equivalent of 0.01 % w/v betaxolol. Mix with the aid of ultrasound for 15 minutes and allow to cool. Centrifuge at a speed of 2000 revolutions per minute for 10 minutes and use the supernatant liquid.
(2) Centrifuge the eye drops at a speed of 25,000 revolutions per minute for 30 minutes and dilute a weighed quantity of the supernatant liquid with sufficient of the mobile phase to produce a solution expected to contain the equivalent of 0.01% w/v of betaxolol.
(3) 0.012% w/v *betaxolol hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS-2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of *water* containing 0.71% w/v *anhydrous disodium hydrogen orthophosphate* and 0.91% w/v of *dimethylamine hydrochloride*, adjusted to pH 3.0 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the eye drops, Appendix V G, and calculate the content of $C_{18}H_{29}O_3$, weight in volume, in solutions (1) and (2) using the declared content of $C_{18}H_{29}O_3$ in *betaxolol hydrochloride BPCRS*. Calculate the content of bound betaxolol from the difference between the contents of betaxolol found in solutions (1) and (2).

LIMITS

45.0 to 65.0% of the stated content of betaxolol

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the eye drops to produce a solution containing the equivalent of 0.01% w/v of betaxolol. Mix thoroughly and centrifuge.

(2) 0.012% w/v of *betaxolol hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Bound betaxolol may be used.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the eye drops, Appendix V G, and calculate the content of $C_{18}H_{29}NO_3$, weight in volume, using the declared content of $C_{18}H_{29}NO_3$ in *betaxolol hydrochloride BPCRS*.

STORAGE

Betaxolol Eye Drops, Suspension should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of betaxolol.

© Crown Copyright 2022

www.webofpharma.com

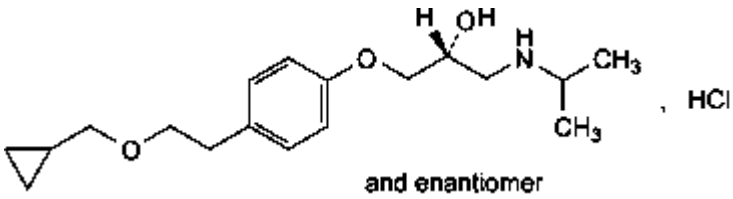
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Betaxolol Hydrochloride

General Notices

(Ph. Eur. monograph 1072)



$C_{18}H_{30}ClNO_3$ 343.9 *63659-19-8*

Action and use

Beta-adrenoceptor antagonist.

Preparations

Betaxolol Eye Drops, Solution

Betaxolol Eye Drops, Suspension

Ph Eur

DEFINITION

(2*RS*)-1-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]propan-2-ol hydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), soluble in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 113 °C to 117 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *betaxolol hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 1 mL of *methanol R*.

Reference solution (a) Dissolve 20 mg of *betaxolol hydrochloride CRS* in 2 mL of *methanol R*.

Reference solution (b) Dissolve 10 mg of *oxprenolol hydrochloride CRS* in 1 mL of reference solution (a).

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *perchloric acid R*, *methanol R*, *water R* (0.5:50:50 *V/V/V*).

Application 2 µL.

Development Over a path of 10 cm.

Drying In air.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with a 50 g/L solution of *vanillin R* in a mixture of 5 volumes of *sulfuric acid R*, 10 volumes of *glacial acetic acid R* and 85 volumes of *methanol R*, heat at 100-105 °C until the colour of the spots reaches maximum intensity (10-15 min), and examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.5 g in water R and dilute to 25 mL with the same solvent.

Acidity or alkalinity

Dissolve 0.20 g in carbon dioxide-free water R and dilute to 20 mL with the same solvent. Add 0.2 mL of methyl red solution R and 0.2 mL of 0.01 M hydrochloric acid. The solution is red. Add 0.4 mL of 0.01 M sodium hydroxide. The solution is yellow.

Related substances

Liquid chromatography (2.2.29). *Prepare reference solutions (c) and (d) immediately before use.*

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (a) Dissolve 8 mg of the substance to be examined and 4 mg of betaxolol impurity A CRS in 20.0 mL of the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 2 mg of betaxolol impurity C CRS in 50 mL of the mobile phase. Dilute 5 mL of the solution to 20 mL with the mobile phase.

Reference solution (d) Dissolve 10 mg of betaxolol for peak identification CRS (containing impurities B, D and E) in 5 mL of reference solution (c).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 175 mL of acetonitrile R and 175 mL of methanol R and dilute to 1 L with a 3.4 g/L solution of potassium dihydrogen phosphate R, previously adjusted to pH 3.0 with phosphoric acid R.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 273 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (d).

Run time 4.5 the retention time of betaxolol.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with betaxolol for peak identification CRS and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B, C, D and E.

Relative retention With reference to betaxolol (retention time = about 8 min): impurity B = about 0.3; impurity A = about 0.8; impurity D = about 1.5; impurity E = about 2.2; impurity C = about 4.1.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity A and betaxolol.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 10.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

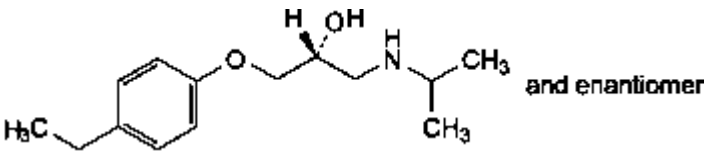
1 mL of *0.1 M sodium hydroxide* is equivalent to 34.39 mg of $C_{18}H_{30}ClNO_3$.

STORAGE

Protected from light.

IMPURITIES

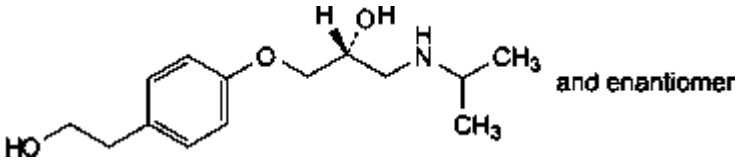
Specified impurities *A, B, C, D, E.*



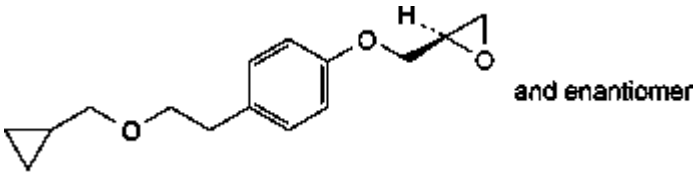
A. (2*RS*)-1-(4-ethylphenoxy)-3-[(1-methylethyl)amino]propan-2-ol,

www.webofpharma.com

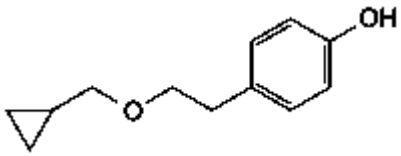
https://thuocngocanh.com/



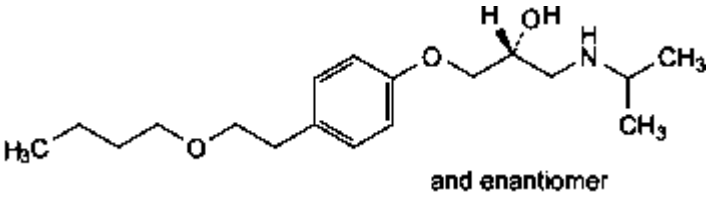
B. (2*RS*)-1-[4-(2-hydroxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,



C. (2*RS*)-2-[[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]methyl]oxirane,



D. 4-[2-(cyclopropylmethoxy)ethyl]phenol,



E. (2*RS*)-1-[4-(2-butoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

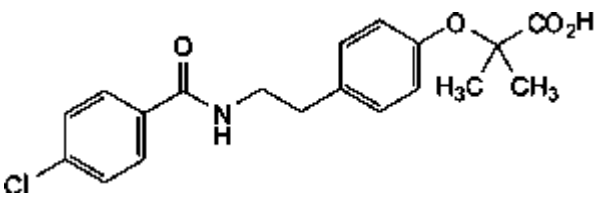
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bezafibrate

General Notices

(Ph. Eur. monograph 1394)



$C_{19}H_{20}ClNO_4$ 361.8 *41859-67-0*

Action and use

Fibrate; lipid-regulating drug.

Preparations

Bezafibrate Tablets

Bezafibrate Prolonged-release Tablets

Ph Eur

DEFINITION

2-[4-[2-[(4-Chlorobenzoyl)amino]ethyl]phenoxy]-2-methylpropanoic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Melting point (2.2.14): 181 °C to 185 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison bezafibrate CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in methanol R and evaporate to dryness. Dry the residues *in vacuo* at 80 °C for 1 h and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methanol R and dilute to 5 mL with the same solvent.

Reference solution Dissolve 10 mg of bezafibrate CRS in methanol R and dilute to 5 mL with the same solvent.

Plate TLC silica gel F_{254} plate R.

Mobile phase glacial acetic acid R, methyl ethyl ketone R, xylene R (2.7:30:60 *V/V/V*).

Application 5 µL.

Development Over half of the plate.

Drying At 120 °C for at least 15 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 1.0 g in dimethylformamide R and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, Method II).

Related substances

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 10.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Reference solution (c) To 1 mL of the test solution, add 1 mL of *0.1 M hydrochloric acid* and evaporate to dryness on a hot plate. Dissolve the residue in 20 mL of the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 40 volumes of a 2.72 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 2.3 with *phosphoric acid R*, and 60 volumes of *methanol R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 228 nm.

Injection 20 µL.

Run time The time necessary to detect the ester, which, depending on the route of synthesis, may be impurity C, D or E.

Relative retention With reference to bezafibrate (retention time = about 6.0 min): impurity A = about 0.5; impurity B = about 0.6; impurity C = about 1.5; impurity D = about 2.3; impurity E = about 6.2.

System suitability:

— *resolution*: minimum 5.0 between the 2 principal peaks in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 5 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.75 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Chlorides (*2.4.4*)

Maximum 300 ppm.

Dilute 10 mL of solution S to 50 mL with *water R*. Filter the resultant suspension through a wet filter previously washed with *water R* until free from chlorides. Prepare the standard using 9 mL of *chloride standard solution (5 ppm Cl) R* and 6 mL of *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

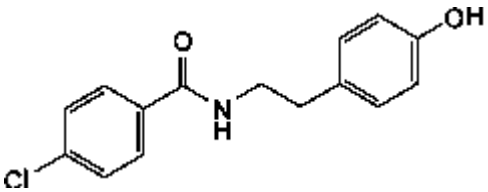
ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 25 volumes of *water R* and 75 volumes of *ethanol (96 per cent) R*. Using 0.1 mL of *phenolphthalein solution R* as indicator, titrate with *0.1 M sodium hydroxide* until a pink colour is obtained. Carry out a blank titration.

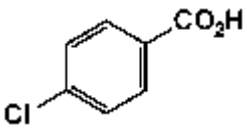
1 mL of *0.1 M sodium hydroxide* is equivalent to 36.18 mg of $C_{19}H_{20}ClNO_4$.

IMPURITIES

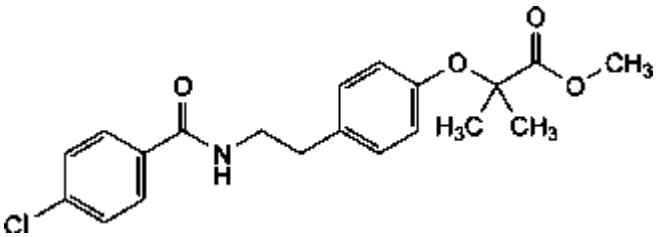
Specified impurities *A, B, C, D, E.*



A. 4-chloro-*N*-[2-(4-hydroxyphenyl)ethyl]benzamide (chlorobenzoyltyramine),



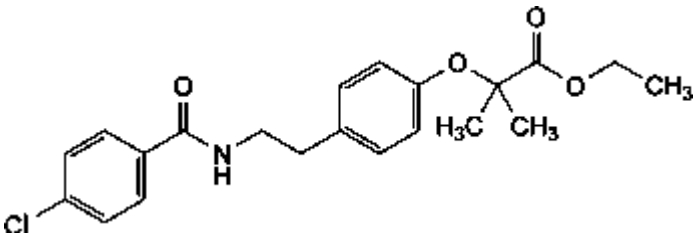
B. 4-chlorobenzoic acid,



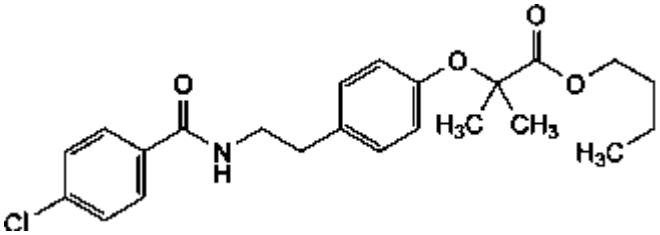
C. methyl 2-[4-[2-[(4-chlorobenzoyl)amino]ethyl]phenoxy]-2-methylpropanoate,

www.webofpharma.com

https://thuvienthuocngocanh.com/



D. ethyl 2-[4-[2-[(4-chlorobenzoyl)amino]ethyl]phenoxy]-2-methylpropanoate,



E. butyl 2-[4-[2-[(4-chlorobenzoyl)amino]ethyl]phenoxy]-2-methylpropanoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bezafibrate Prolonged-release Tablets

General Notices

Prolonged-release Bezafibrate Tablets

Bezafibrate Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Fibrate; lipid-regulating drug.

DEFINITION

Bezafibrate Prolonged-release Tablets contain Bezafibrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of bezafibrate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bezafibrate, $C_{19}H_{20}ClNO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.2 g of Bezafibrate with two 10-mL quantities of *acetone* for 10 minutes, filter the combined extracts (Whatman GF/C is suitable) and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of Bezafibrate *(RS 419)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 100 mg of Bezafibrate with 15 mL of *methanol* for 2 minutes, shake for a further 10 minutes, cool, add sufficient mobile phase to produce 100 mL, mix and filter, discarding the first 20 mL of

www.webofpharma.com

https://thuocngocanh.com/

filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) Dissolve sufficient quantities of *bezafibrate BPCRS* and *chlorobenzoyltyramine BPCRS* in the minimum quantity of *methanol* and dilute with mobile phase to produce a solution containing 0.0002% w/v of *bezafibrate BPCRS* and 0.0002% w/v of *chlorobenzoyltyramine BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

The retention time of bezafibrate is about 5 minutes. Allow the chromatography to proceed for four times the retention time of the principal peak.

MOBILE PHASE

A mixture of 3.9 volumes of a 40% w/v solution of *tetrabutylammonium hydroxide*, 400 volumes of *acetonitrile* and 600 volumes of *water*, adjusting the final pH to 4.0 with 10% v/v *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to bezafibrate and chlorobenzoyltyramine is at least 7.0. If necessary adjust the content of tetrabutylammonium hydroxide to obtain the required resolution.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the total area of any such peaks is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.01%).

ASSAY

Weigh and powder 20 tablets. For solution (1) mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Bezafibrate with 70 mL of *methanol* for 2 minutes, shake for a further 10 minutes, cool, add sufficient *methanol* to produce 100 mL, mix and filter discarding the first 20 mL of filtrate. Dilute 1 volume to 100 volumes with *methanol*. Solution (2) is a 0.001% w/v solution of *bezafibrate BPCRS* in *methanol*.

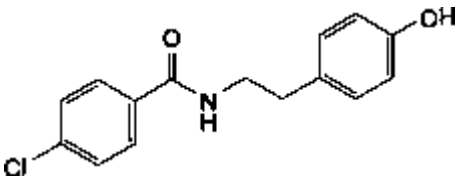
www.webofpharma.com

https://thuocngocanh.com/

Measure the *absorbance* of the resulting solutions at the maximum at about 230 nm, Appendix II B. Calculate the content of $C_{19}H_{20}ClNO_4$ from the declared content of $C_{19}H_{20}ClNO_4$ in *bezafibrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include:



4-chloro-*N*-[2-(4-hydroxyphenyl)ethyl]benzamide (chlorobenzoyltyramine).

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bezafibrate Tablets

General Notices

Action and use

Fibrate; lipid-regulating drug.

DEFINITION

Bezafibrate Tablets contain Bezafibrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bezafibrate, $C_{19}H_{20}ClNO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.2 g of Bezafibrate with two 10-mL quantities of *acetone* for 10 minutes, combine and filter the extracts (a Whatman GF/C is suitable) and evaporate the filtrate to dryness. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of bezafibrate *(RS 419)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use as the medium, at a temperature of 37°, 900 mL of a pH 6.5 buffer solution prepared by dissolving 0.608 g of *sodium hydroxide* and 6.805 g of *potassium dihydrogen orthophosphate* in sufficient *water* to produce 1000 mL and adjusting the pH to 6.5 ± 0.05 using *sodium hydroxide solution* or *orthophosphoric acid*.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium, filter and dilute 1 volume of the filtrate to 20 volumes with the dissolution medium and measure the *absorbance* at the maximum at 229 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0011% w/v solution of *bezafibrate BPCRS* in the dissolution medium using dissolution medium in the reference cell.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of bezafibrate, $C_{19}H_{20}ClNO_4$, in the medium from the absorbances obtained and using the declared content of $C_{19}H_{20}ClNO_4$ in *bezafibrate BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 100 mg of Bezafibrate with 15 mL of *methanol* for 2 minutes, shake for a further 10 minutes, cool, add sufficient of the mobile phase to produce 100 mL, mix and filter, discarding the first 20 mL of filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

(4) Dissolve sufficient quantities of *bezafibrate BPCRS* and *chlorobenzoyltyramine BPCRS* in the minimum quantity of *methanol* and dilute with mobile phase to produce a solution containing 0.0002% w/v of *bezafibrate BPCRS* and 0.0002% w/v of *chlorobenzoyltyramine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

(g) The retention time of bezafibrate is about 5 minutes. Allow the chromatography to proceed for four times the retention time of the principal peak.

MOBILE PHASE

3.9 volumes of 40% w/v of *tetrabutylammonium hydroxide*, 400 volumes of *acetonitrile* and 600 volumes of *water* and adjusting the final pH to 4.0 with 10% v/v *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to bezafibrate and chlorobenzoyltyramine is at least 7.0. If necessary, adjust the content of tetrabutylammonium hydroxide to obtain the required resolution.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the total area of any such peaks is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%).

www.webofpharma.com

https://thuocngocanh.com/

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.05%).

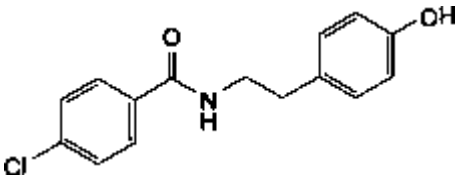
ASSAY

Weigh and powder 20 tablets. For solution (1) mix with the aid of ultrasound a quantity of the powdered tablets containing 100 mg of Bezafibrate with 70 mL of *methanol* for 2 minutes, shake for a further 10 minutes, cool, add sufficient *methanol* to produce 100 mL, mix and filter discarding the first 20 mL of filtrate; dilute 1 volume of the filtrate to 100 volumes with *methanol*. Solution (2) contains 0.001% w/v of *bezafibrate BPCRS* in *methanol*.

Measure the *absorbance* at the maximum at 229 nm, Appendix II B. Calculate the content of $C_{19}H_{20}ClNO_4$ in the tablets from the absorbances obtained and from the declared content of $C_{19}H_{20}ClNO_4$ in *bezafibrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include,



4-chloro-*N*-[2-(4-hydroxyphenyl)ethyl]benzamide (chlorobenzoyltyramine).

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

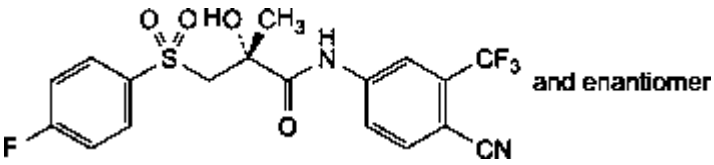
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bicalutamide

General Notices

(Ph. Eur. monograph 2196)



$C_{18}H_{14}F_4N_2O_4S$ 430.4 *90357-06-5*

Action and use

Antiandrogen; treatment of prostate cancer.

Preparation

Bicalutamide Tablets

Ph Eur

DEFINITION

(2*RS*)-*N*-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in acetone, slightly soluble in anhydrous ethanol and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison bicalutamide CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture phosphoric acid R, acetonitrile R1, water R (0.05:50:50 *V/V/V*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of bicalutamide for system suitability CRS (containing impurities B and C) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (c) Dissolve 25.0 mg of bicalutamide CRS in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: spherical end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: phosphoric acid R, acetonitrile R1, water R (1.9:100:1900 *V/V/V*);

— *mobile phase B*: phosphoric acid R, water R, acetonitrile R1 (1.9:100:1900 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	92	8
3 - 23	92 → 67	8 → 33
23 - 43	67 → 50	33 → 50

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
43 - 50	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *bicalutamide for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to bicalutamide (retention time = about 38 min): impurity B = about 0.98; impurity C = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to bicalutamide.

Limits:

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{18}H_{14}F_4N_2O_4S$ taking into account the assigned content of *bicalutamide CRS*.

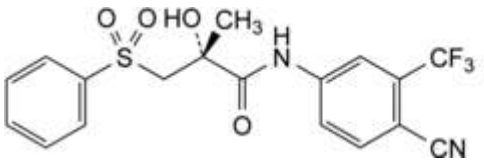
www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

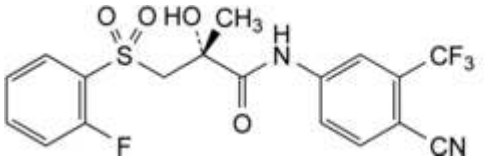
Specified impurities C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D, E, F, H, J, K, L, M.



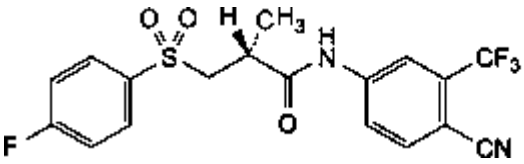
and enantiomer

A. (2*RS*)-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methyl-3-(phenylsulfonyl)propanamide,



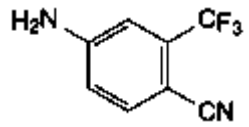
and enantiomer

B. (2*RS*)-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(2-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide,

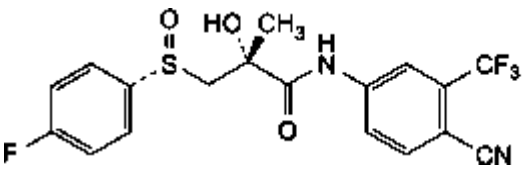


and enantiomer

C. (2*RS*)-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-methylpropanamide,

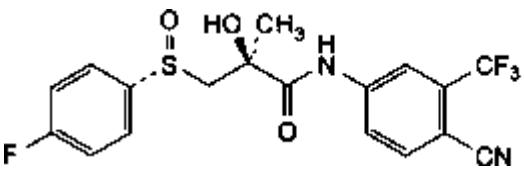


D. 4-amino-2-(trifluoromethyl)benzonitrile,



and enantiomer

E. (2*RS*)-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(*RS*)-(4-fluorophenyl)sulfinyl]-2-hydroxy-2-methylpropanamide,

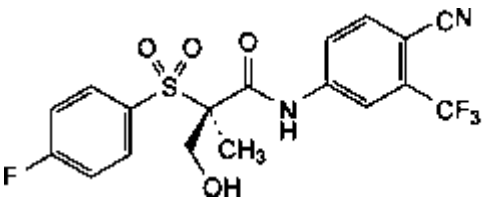


and enantiomer

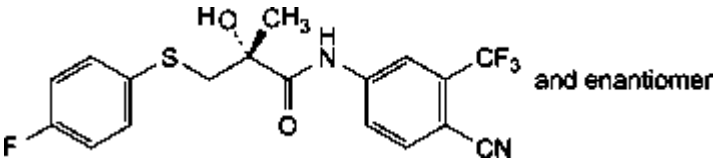
www.webofpharma.com

https://thuocngocanh.com/

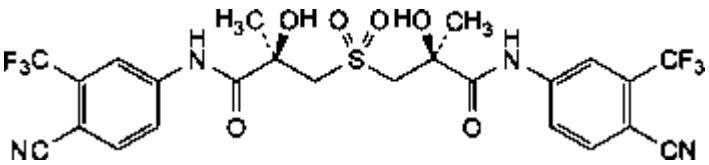
F. (2*SR*)-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(*RS*)-(4-fluorophenyl)sulfinyl]-2-hydroxy-2-methylpropanamide,



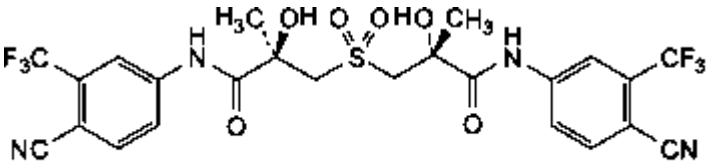
H. (2*RS*)-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-[(4-fluorophenyl)sulfonyl]-3-hydroxy-2-methylpropanamide,



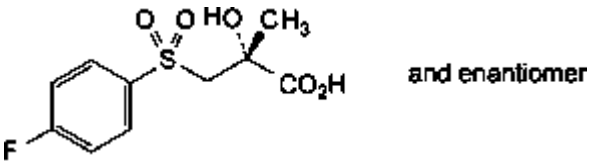
J. (2*RS*)-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfanyl]-2-hydroxy-2-methylpropanamide,



K. (2*R*,2′*S*)-3,3′-sulfonylbis[*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methylpropanamide],



L. (2*RS*,2′*RS*)-3,3′-sulfonylbis[*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methylpropanamide],



M. (2*RS*)-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanoic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bicalutamide Tablets

General Notices

Action and use

Antiandrogen; treatment of prostate cancer.

DEFINITION

Bicalutamide Tablets contain Bicalutamide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bicalutamide, $C_{18}H_{14}F_4N_2O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 0.1 g of Bicalutamide add 10 mL of *acetone*, shake and centrifuge. Filter the supernatant liquid (Whatman GF/C filter is suitable) and evaporate to dryness under a stream of nitrogen at 40° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of bicalutamide (*RS 466*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a 1.0% w/v solution of *sodium dodecyl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with *water* if necessary, to produce a solution expected to contain 0.0056% w/v of Bicalutamide, at the maximum at 272 nm, Appendix II B using the dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0056% w/v solution of *bicalutamide BPCRS* using the dissolution medium in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of bicalutamide, $C_{18}H_{14}F_4N_2O_4S$ in the medium from the absorbances obtained and using the declared content of $C_{18}H_{14}F_4N_2O_4S$ in *bicalutamide BPCRS*.

LIMITS

The amount of bicalutamide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Prepare a mixture of 0.5 volumes *orthophosphoric acid*, 500 volumes of *acetonitrile R1* and 500 volumes of *water* (solvent A).

(1) Dissolve a quantity of the powdered tablets containing 25 mg of Bicalutamide in solvent A with the aid of ultrasound. Add sufficient solvent A to produce a solution containing 0.1% w/v of Bicalutamide and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A. Dilute 1 volume of this solution to 10 volumes.
(3) Dissolve 5 mg of *bicalutamide for system suitability EPCRS* (containing impurities B and C) in solvent A and dilute to 5.0 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1.9 volumes of *orthophosphoric acid*, 100 volumes of *acetonitrile R1* and 1900 volumes of *water*.

Mobile phase B 1.9 volumes of *orthophosphoric acid*, 100 volumes of *water* and 1900 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	92	8	isocratic
3-23	92→67	8→33	linear gradient
23-43	67→50	33→50	linear gradient
43-55	50	50	isocratic
55-56	50→92	50→8	linear gradient
56-60	92	8	re-equilibration

Use the chromatogram supplied with *bicalutamide for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify the peaks due to impurities B and C.

www.webofpharma.com

https://thuocngocanh.com/

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to bicalutamide (retention time about 38 minutes) are: impurity D, about 0.7; .impurity B, about 0.98 and impurity C, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the peak to valley ratio is at least 2.5, where H_p is the height above the baseline of the peak due to impurity B and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bicalutamide.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Prepare a mixture of 40 volumes of *water* and 60 volumes of *acetonitrile* (solvent B).

(1) To a quantity of the powdered tablets containing 0.25 g of Bicalutamide, add 40 mL of *water* and mix with the aid of ultrasound, add sufficient *acetonitrile* to produce 100 mL and mix. Centrifuge and dilute 1 volume of the supernatant liquid to 25 volumes with solvent B.
(2) 0.01% w/v of *bicalutamide BPCRS* in solvent B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapak C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 270 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

1 volume of *trifluoroacetic acid*, 350 volumes of *acetonitrile* and 650 volumes of *water*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency* determined on the peak due to bicalutamide is at least 2000 *theoretical plates*.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{14}F_4N_2O_4S$ in the tablets using the declared content of $C_{18}H_{14}F_4N_2O_4S$ in *bicalutamide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Bicalutamide.

© Crown Copyright 2022

www.webofpharma.com

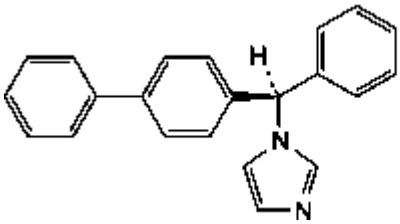
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bifonazole

General Notices

(Ph. Eur. monograph 1395)



and enantiomer

$C_{22}H_{18}N_2$ 310.4 *60628-96-8*

Action and use

Antifungal.

Ph Eur

DEFINITION

1-[(*RS*)-(Biphenyl-4-yl)phenylmethyl]-1*H*-imidazole.

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *bifonazole CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *2-propanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution pH 3.2 Mix 2.0 mL of *phosphoric acid R* with 980 mL of *water R*, adjust to pH 3.2 (*2.2.3*) with *triethylamine R* and dilute to 1000.0 mL with *water R*.

Test solution Dissolve 50.0 mg of the substance to be examined in 25 mL of *acetonitrile R* and dilute to 50.0 mL with buffer solution pH 3.2.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with buffer solution pH 3.2. Dilute 1.0 mL of this solution to 10.0 mL with buffer solution pH 3.2.

Reference solution (b) Dissolve 2 mg of *bifonazole for system suitability CRS* (containing impurities A, B, C, D and E) in 2 mL of *acetonitrile R* and dilute to 10.0 mL with buffer solution pH 3.2.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, buffer solution pH 3.2 (20:80 *V/V*);

— *mobile phase B*: buffer solution pH 3.2, *acetonitrile R1* (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	60	40
8 - 12	60 → 10	40 → 90
12 - 30	10	90

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 50 µL.

Identification of impurities Use the chromatogram supplied with *bifonazole for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and E.

Relative retention With reference to bifonazole (retention time = about 4 min): impurity C = about 0.2; impurity B = about 0.7; impurity A = about 3.2; impurity D = about 3.6; impurity E = about 5.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity B and bifonazole.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2;

— *impurities B, D*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities A, C*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity E*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 80 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

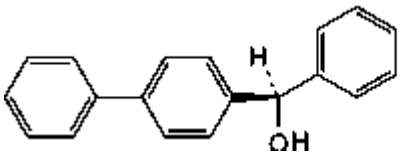
1 mL of *0.1 M perchloric acid* is equivalent to 31.04 mg of $C_{22}H_{18}N_2$.

IMPURITIES

www.webofpharma.com

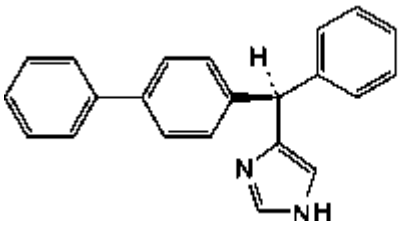
https://thuocngocanh.com/

Specified impurities *A, B, C, D, E.*



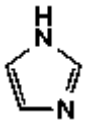
and enantiomer

A. (*RS*)-(biphenyl-4-yl)phenylmethanol,

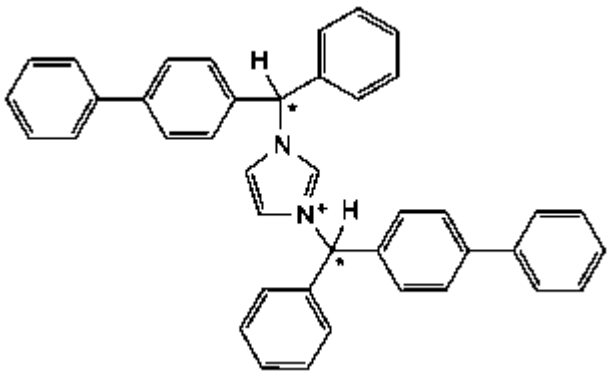


and enantiomer

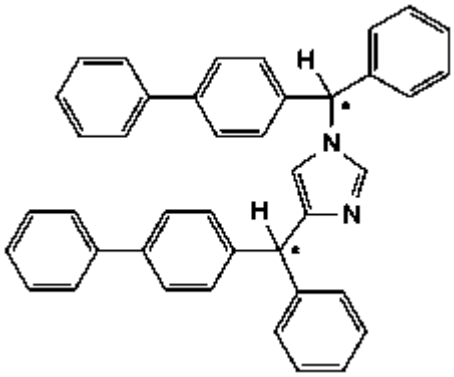
B. 4-[(*RS*)-(biphenyl-4-yl)phenylmethyl]-1*H*-imidazole,



C. 1*H*-imidazole,



D. 1,3-bis[(biphenyl-4-yl)phenylmethyl]-1*H*-imidazolium ion,



E. 1,4-bis[(biphenyl-4-yl)phenylmethyl]-1*H*-imidazole.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

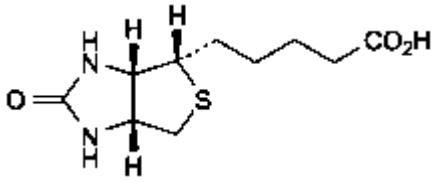
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Biotin

General Notices

(Ph. Eur. monograph 1073)



$C_{10}H_{16}N_2O_3S$ 244.3 *58-85-5*

Action and use

Vitamin.

Ph Eur

DEFINITION

5-[(3a*S*,4*S*,6a*R*)-2-Oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]pentanoic acid.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very slightly soluble in water and in ethanol (96 per cent), practically insoluble in acetone. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A.

Second identification: B.

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *biotin CRS*.

B. Thin-layer chromatography (2.2.27).

Prepare the solutions immediately before use and keep protected from bright light.

Test solution Dissolve 5 mg of the substance to be examined in *glacial acetic acid R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 5 mg of *biotin CRS* in *glacial acetic acid R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R* (5 µm).

Mobile phase *methanol R*, *glacial acetic acid R*, *toluene R* (5:25:75 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In a current of warm air.

Detection Allow to cool and spray with *4-dimethylaminocinnamaldehyde solution R*; examine immediately in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 0.250 g in a 4 g/L solution of *sodium hydroxide R* and dilute to 25.0 mL with the same alkaline solution.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Specific optical rotation (2.2.7)

+ 89 to + 93 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and keep protected from bright light.*

Solvent mixture *water R*, *acetonitrile R* (50:50 *V/V*).

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture using sonication and dilute to 50.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *biotin for system suitability CRS* (containing impurities A, C and E) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *methanesulfonic acid R*, *acetonitrile R1*, *water for chromatography R* (1:25:1000 *V/V/V*);

— *mobile phase B*: *methanesulfonic acid R*, *water for chromatography R*, *acetonitrile R1* (1:25:1000 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 20	95 → 0	5 → 100
20 - 28	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm from 0 to 5 min and at 210 nm from 5 to 28 min.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *biotin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, C and E.

Relative retention With reference to biotin (retention time = about 12 min): bromide = about 0.2; impurity C = about 0.25; impurity A = about 1.1; impurity E = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to biotin and impurity A.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity E by 0.2;

www.webofpharma.com

https://thuocngocanh.com/

— for each impurity, use the concentration of biotin in reference solution (a).

Limits:

— *impurities A, E*: for each impurity, maximum 0.5 per cent;

— *impurity C*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent, disregard the peak due to the bromide ion.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Suspend 0.200 g in 5 mL of *dimethylformamide R*. Heat until the substance has dissolved completely. Add 50 mL of *ethanol R* and titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M tetrabutylammonium hydroxide* is equivalent to 24.43 mg of $C_{10}H_{16}N_2O_3S$.

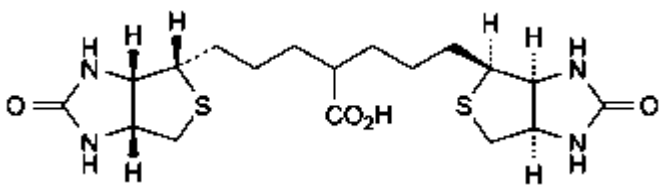
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, C, E.*

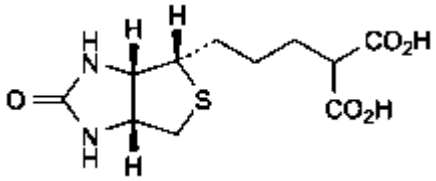
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, F, G, H.*



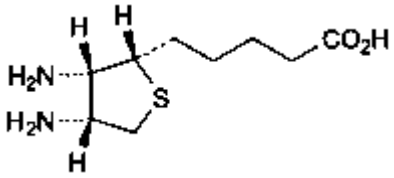
www.webofpharma.com

https://thuocngocanh.com/

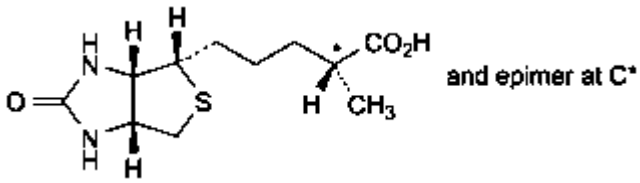
A. 5-[(3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]-2-[[(3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]propyl]pentanoic acid,



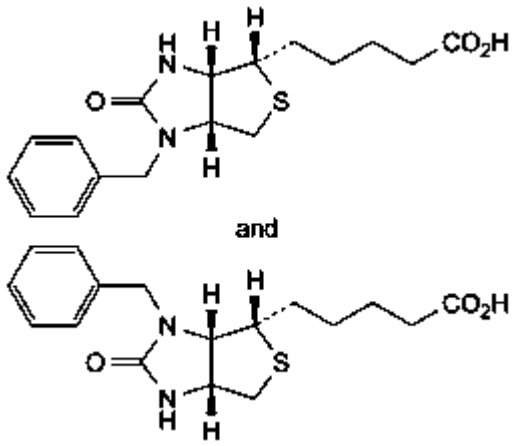
B. 4-[(3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]butane-1,1-dicarboxylic acid,



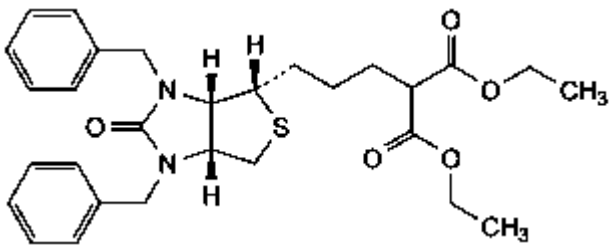
C. 5-[(2*S*,3*S*,4*R*)-3,4-diaminothiolan-2-yl]pentanoic acid,



D. (2*RS*)-2-methyl-5-[(3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]pentanoic acid,



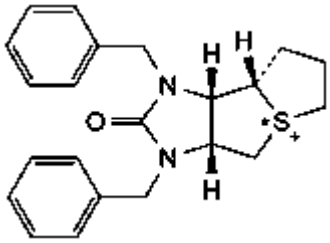
E. 5-[(3a*S*,4*S*,6a*R*)-1-benzyl-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]pentanoic acid and 5-[(3a*S*,4*S*,6a*R*)-3-benzyl-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]pentanoic acid,



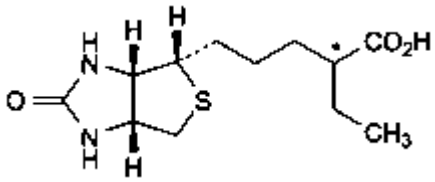
www.webofpharma.com

https://thuocngocanh.com/

F. diethyl 4-[(3a*S*,4*S*,6a*R*)-1,3-dibenzyl-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]butane-1,1-dicarboxylate,



G. (3a*R*,8a*S*,8b*S*)-1,3-dibenzyl-2-oxodecahydrothieno[1′,2′:1,2]thieno[3,4-*d*]imidazol-5-ium,



H. 2-ethyl-5-[(3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]pentanoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

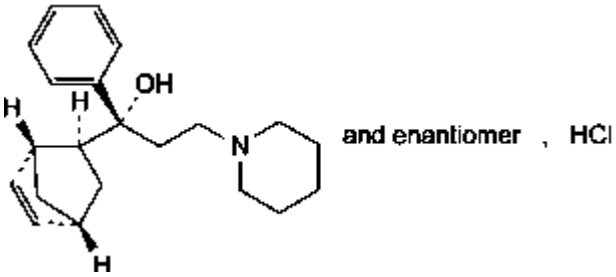
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Biperiden Hydrochloride

General Notices

(Ph. Eur. monograph 1074)



$C_{21}H_{30}ClNO$ 347.9 *1235-82-1*

Action and use

Anticholinergic.

Ph Eur

DEFINITION

(1*RS*)-1-[(1*RS*,2*SR*,4*RS*)-Bicyclo[2.2.1]hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water and in ethanol (96 per cent), very slightly soluble in methylene chloride.

mp

About 280 °C, with decomposition.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *biperiden hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *biperiden hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *biperiden impurity A CRS* in reference solution (a) and dilute to 2 mL with the same solution.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *diethylamine R*, *methanol R*, *toluene R* (1:1:20 *V/V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *dilute potassium iodobismuthate solution R* and then with *sodium nitrite solution R* and examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

C. To about 20 mg add 5 mL of *phosphoric acid R*. A green colour develops.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.10 g in *carbon dioxide-free water R*, heating gently if necessary, and dilute to 50 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.0 to 6.5 for solution S.

Related substances

Gas chromatography (*2.2.28*).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 0.5 mL of the test solution to 100 mL with *methanol R*. Dilute 10 mL of this solution to 50 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *biperiden impurity A CRS* in *methanol R* and dilute to 5 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *methanol R*.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.25 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 0.4 mL/min.

Split ratio 1:250.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	200
	5 - 40	200 → 270
Injection port		250
Detector		300

Detection Flame ionisation.

Injection 2 µL.

www.webofpharma.com

https://thuocngocanh.com/

Run time Twice the retention time of biperiden.

Relative retention With reference to biperiden: impurities A, B and C = between 0.95 and 1.05.

System suitability:

— *resolution*: minimum 2.5 between the peak due to biperiden (1st peak) and the peak due to impurity A (2nd peak) in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 6 for the principal peak in the chromatogram obtained with reference solution (a).

Limits:

— *impurities A, B, C*: for each impurity, maximum 0.50 per cent of the area of the principal peak;

— *any other impurity*: for each impurity, maximum 0.10 per cent of the area of the principal peak;

— *total of impurities A, B and C*: maximum 1.0 per cent of the area of the principal peak;

— *total of impurities other than A, B and C*: maximum 0.50 per cent of the area of the principal peak;

— *disregard limit*: 0.05 per cent of the area of the principal peak.

Impurity F (*2.4.24*)

Maximum 2 ppm.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 60 mL of *ethanol (96 per cent) R*. In a closed vessel, titrate with *0.1 M alcoholic potassium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M alcoholic potassium hydroxide* is equivalent to 34.79 mg of $C_{21}H_{30}ClNO$.

STORAGE

In an airtight container, protected from light.

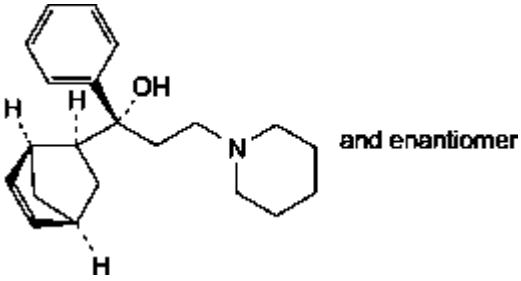
IMPURITIES

Specified impurities *A, B, C, F.*

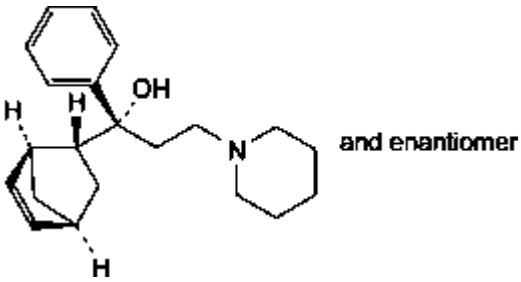
www.webofpharma.com

https://thuvienthuocngocanh.com/

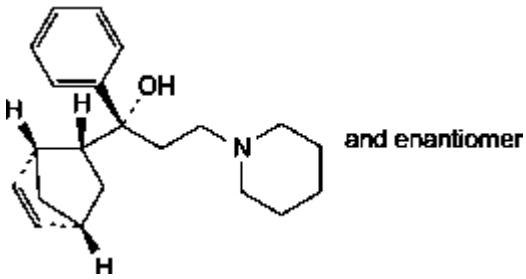
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, E.



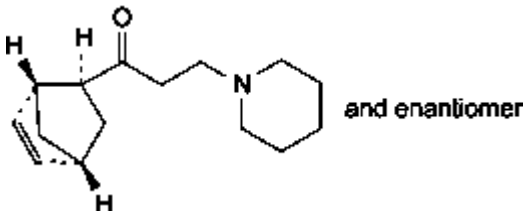
A. (1*RS*)-1-[(1*SR*,2*SR*,4*SR*)-bicyclo[2.2.1]hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol (*endo* form),



B. (1*RS*)-1-[(1*SR*,2*RS*,4*SR*)-bicyclo[2.2.1]hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol,



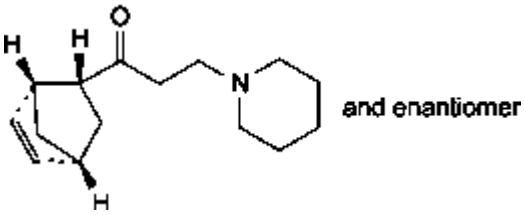
C. (1*RS*)-1-[(1*RS*,2*RS*,4*RS*)-bicyclo[2.2.1]hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl)propan-1-ol,



D. 1-[(1*RS*,2*SR*,4*RS*)-bicyclo[2.2.1]hept-5-en-2-yl]-3-(piperidin-1-yl)propan-1-one,

www.webofpharma.com

https://thuvienthuocngocanh.com/



E. 1-[(1*RS*,2*RS*,4*RS*)-bicyclo[2.2.1]hept-5-en-2-yl]-3-(piperidin-1-yl)propan-1-one,

F. benzene.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Biphasic Insulin Aspart Injection

General Notices

Action and use

Hormone; treatment of diabetes mellitus.

DEFINITION

Biphasic Insulin Aspart Injection is a sterile buffered suspension of Insulin Aspart complexed with Protamine Sulfate in a solution of Insulin Aspart.

The injection complies with the requirements stated under Injectable Insulin Preparations, with the exception of the test for insulin in the supernatant, and with the following requirements.

Content of insulin aspart, $C_{256}H_{381}N_{65}O_{79}S_6$

90.0 to 110.0% of the stated amount of insulin aspart, $C_{256}H_{381}N_{65}O_{79}S_6$, together with B28isoAsp insulin aspart, A21Asp insulin aspart, B3Asp insulin aspart and B3isoAsp insulin aspart (determined as the total content of soluble Insulin Aspart and Insulin Aspart complexed with Protamine Sulfate).

Content of soluble insulin aspart, $C_{256}H_{381}N_{65}O_{79}S_6$

Stated content of Soluble Insulin Aspart (%)	Stated content of Protamine complexed Insulin Aspart (%)	Acceptable Range (%)
30	70	24 to 36
50	50	42 to 58
70	30	62 to 78

CHARACTERISTICS

A white or almost white suspension which deposits a white or almost white sediment and leaves a colourless or almost colourless supernatant liquid; the sediment is readily re-suspended by gentle shaking. When examined under a microscope, the particles are seen to be rod-shaped crystals, the majority with a maximum dimension greater than 1 µm but rarely exceeding 60 µm, free from large aggregates.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

In the Assay for insulin aspart, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Related proteins

Carry out the method for *liquid chromatography*, Appendix III D, as described under Assay for insulin aspart using the *normalisation procedure*.

LIMITS

In the chromatogram obtained with solution (1):

the area of the peak corresponding to B28isoAsp insulin aspart is not greater than 2.5%;

the total area of the peaks corresponding to A21Asp insulin aspart, B3Asp insulin aspart and B3isoAsp insulin aspart is not greater than 5.0%;

the total area of any other *secondary peaks* is not greater than 3.5%;

disregard any peaks due to protamine and preservatives.

Total zinc

Not more than 40 µg per 100 units of Insulin Aspart, determined by *atomic absorption spectrometry*, Appendix II D, Method I.

Test solution Shake the preparation gently and dilute a volume containing 100 units of insulin aspart to 25.0 mL with 0.01M *hydrochloric acid*. Dilute, if necessary, to a suitable concentration of zinc (for example 0.00001% w/v to 0.0001% w/v of Zn) with 0.01M *hydrochloric acid*.

Reference solutions Use solutions containing 0.00002% w/v, 0.00004% w/v, 0.00006% w/v, 0.00008% w/v and 0.0001% w/v of Zn, freshly prepared by diluting *zinc standard solution (0.5% w/v of Zn)* with 0.01M *hydrochloric acid*.

Measure the absorbance at 213.9 nm using a zinc hollow-cathode lamp as source of radiation and an air-acetylene flame of suitable composition (for example 11 litres of air and 2 litres of acetylene per minute).

ASSAY

For insulin aspart

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, maintained at 2° to 8°.

(1) Dilute, if necessary, the preparation being examined with 0.01M *hydrochloric acid* to produce a solution containing 100 units/mL of insulin aspart (equivalent to approximately 0.35% w/v insulin aspart). Add 4 µL of *6M hydrochloric acid* per mL to this solution to obtain a clear solution. Use the solution within 48 hours.

(2) Dissolve the contents of a vial of *insulin aspart EPCRS* in 0.01M *hydrochloric acid* to produce a solution containing 0.4% w/v insulin aspart. Use the solution within 48 hours.

www.webofpharma.com

https://thuocngocanh.com/

(3) Use an appropriate solution with a content of B3Asp insulin aspart and A21Asp insulin aspart of not less than 1 per cent. This may be achieved by storing solution (2) at room temperature for up to 3 days. Maintain the solution at 2-8 °C and use within 72 hours.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 214 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 70 g of *anhydrous sodium sulfate* in approximately 4500 mL of *water*; add 6.5 mL of *orthophosphoric acid* and adjust to pH 3.4, if necessary, with *dilute sodium hydroxide solution*. Dilute to 5000 mL with *water*; filter and degas. Mix 9 volumes of the solution with 1 volume of *acetonitrile R1*.

Mobile phase B Equal volumes of *water* and *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0-35	58	42	Isocratic
35-40	58 → 20	42 → 80	Linear gradient
40-45	20	80	Isocratic
45-46	20 → 58	80 → 42	Linear gradient
46-60	58	42	Re-equilibration

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to insulin aspart (retention time, 20 to 26 minutes) are: B28isoAsp insulin aspart, about 0.9; B3Asp insulin aspart which may co-elute with A21Asp insulin aspart, about 1.3; B3isoAsp insulin aspart, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peak due to insulin aspart and the peak due to A21Asp insulin aspart plus B3Asp insulin aspart is at least 1.6;

in the chromatogram obtained with solution (2), the *symmetry factor* of the principal peak is not more than 1.8.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of insulin aspart, $C_{256}H_{381}N_{65}O_{79}S_6$, using the chromatograms obtained with solution (1) and solution (2) and the declared content of insulin aspart in *insulin aspart EPCRS*.

For soluble insulin aspart

Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions, maintained at 2° to 8°.

Solution A A solution containing 6.05% w/v of *tris(hydroxymethyl)aminomethane*, 4.50% w/v of *disodium edetate* and 1.80% v/v of 4M *hydrochloric acid* in *water* (the pH of the final solution should be about 8.6).

(1) Transfer the re-suspended contents of one container to a centrifuge tube. Add 50 µL of solution A per 3 mL of sample and mix for 5 seconds using a vortex mixer. Stopper the tube and allow to stand at 25º for 1 hour. Centrifuge for 10 minutes at 1500 *g* at a temperature of 21º to 25º and retain the supernatant liquid. Repeat the process beginning at the words 'Add 50 µL of solution A…' and retain the supernatant liquid. Add 4 µL of *6M hydrochloric acid* per mL of the clear supernatant liquid and mix thoroughly.
(2) To the contents of one container add 4 µL of *6M hydrochloric acid* per mL of sample and mix thoroughly.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 7.8 mm) packed with *hydrophilic silica gel for chromatography* (10 µm) (Waters Insulin HMWP column is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 50 µL of each solution.
(g) Allow the chromatography to proceed for 2.5 times the retention time of insulin aspart.

MOBILE PHASE

2.5M acetic acid.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), *the column efficiency*, determined on the peak due to insulin aspart, is at least 1000 theoretical plates.

DETERMINATION OF CONTENT

Calculate the content of soluble insulin aspart using the following equation:

$$\frac{A_{solution\ (1)} \times (3000 + 50)}{A_{solution\ (2)} \times 3000} \times 100\%$$

where,

www.webofpharma.com

https://thuocngocanh.com/

$A_{solution\ (1)}$ = area of the principal peak in the chromatogram obtained with solution (1)

$A_{solution\ (2)}$ = area of the principal peak in the chromatogram obtained with solution (2)

LABELLING

The label states: (1) the ratio of soluble insulin aspart to insulin aspart protamine suspension used in the manufacturing process of biphasic insulin aspart injection; (2) the potency in units per mL.

100 units are equivalent to 3.50 mg of insulin aspart.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Biphasic Insulin Lispro Injection

General Notices

Action and use

Hormone; treatment of diabetes mellitus.

DEFINITION

Biphasic Insulin Lispro Injection is a sterile buffered suspension of Insulin Lispro complexed with Protamine Sulfate in a solution of Insulin Lispro.

The injection complies with the requirements stated under Injectable Insulin Preparations, with the exception of the test for Insulin in the supernatant, and with the following requirements.

Content of insulin lispro, $C_{257}H_{383}N_{65}O_{77}S_6$

90.0 to 105.0% of the stated amount (determined as the total content of soluble Insulin Lispro and Insulin Lispro complexed with Protamine Sulfate).

Content of soluble insulin lispro, $C_{257}H_{383}N_{65}O_{77}S_6$

Stated content of soluble Insulin Lispro (%)	Stated content of Protamine complexed Insulin Lispro (%)	Acceptable Range (%)
25	75	15 to 30
50	50	40 to 55

CHARACTERISTICS

A white or almost white suspension which deposits a white or almost white sediment and leaves a colourless or almost colourless supernatant liquid; the sediment is readily re-suspended by gentle shaking. When examined under a microscope, the particles are seen to be rod-shaped crystals, the majority with a maximum dimension greater than 1 µm but rarely exceeding 60 µm, free from large aggregates.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

In the Assay for insulin lispro, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Impurities with molecular masses greater than that of insulin lispro

Carry out the test for Impurities with molecular masses greater than that of insulin under *Injectable Insulin Preparations*.

LIMITS

the sum of the areas of the peaks in the chromatogram obtained with the test solution with a retention time less than that of the principal peak is not more than 1.5% of the total area of the peaks.

Disregard any peak with a retention time greater than that of the peak due to insulin lispro monomer.

Related proteins

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*.

(1) Dilute, if necessary, the preparation being examined with 0.01M *hydrochloric acid* to produce a solution containing 0.35% w/v of insulin lispro. Add 4 µL of *6M hydrochloric acid* per mL of this solution. Maintain the solution at 2° to 8° and use within 56 hours.
(2) Prepare a 0.35% w/v solution of insulin lispro in 0.01M *hydrochloric acid* and add 4 µL of *6M hydrochloric acid* per mL. Allow to stand at room temperature to obtain a solution containing between 0.8% and 11% of A21 desamido insulin lispro.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) with a pore size of 30 nm (Vydac Protein and Peptide C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 214 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 82 volumes of a 2.84% w/v solution of *anhydrous sodium sulfate* adjusted to pH 2.3 with *orthophosphoric acid* and 18 volumes of *acetonitrile for chromatography*.

Mobile phase B Equal volumes of a 2.84% w/v solution of *anhydrous sodium sulfate*, adjusted to pH 2.3 with *orthophosphoric acid*, and *acetonitrile for chromatography*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0-60	81	19	Isocratic
60-83	81 → 51	19 → 49	Linear gradient
83-84	51 → 81	49 → 19	Linear gradient
84-94	81	19	Re-equilibration

SYSTEM SUITABILITY

Adjust the mobile phase composition to obtain a retention time of about 41 minutes for insulin lispro; A21 desamido insulin lispro elutes near the start of the gradient elution.

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the first peak (insulin lispro) and the second peak (A21 desamido insulin lispro) is at least 1.5;

in the chromatogram obtained with solution (2) the *symmetry factor* for the peak due to insulin lispro is less than 2.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (3) due to A21 desamido insulin lispro.

In the chromatogram obtained with solution (1):

the amount of A21 desamido insulin lispro is not more than 1.5%;

the total amount of related proteins (excluding A21) is not greater than 4.0%;

disregard any peak due to protamine and any peak not greater than 0.1%.

Total zinc

14 to 35 µg per 100 units of Insulin Lispro, determined by *atomic absorption spectrometry*, Appendix II D, Method I.

Test solution Shake the preparation gently and dilute a volume containing 200 units of insulin lispro to 25.0 mL with 0.01M *hydrochloric acid*. Dilute if necessary to a suitable concentration of zinc (for example 0.00004% w/v to 0.00016%w/v of Zn) with 0.01M *hydrochloric acid*.

Reference solutions Use solutions containing 0.00004% w/v, 0.00008% w/v, 0.0001% w/v, 0.00012% w/v and 0.00016%w/v of Zn per mL, freshly prepared by diluting *zinc standard solution (0.5% w/v of Zn)* with 0.01M *hydrochloric acid*.

Measure the absorbance at 213.9 nm using a zinc hollow-cathode lamp as source of radiation and an air-acetylene flame of suitable composition (for example 11 litres of air and 2 litres of acetylene per minute).

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

For insulin lispro

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute, if necessary, the preparation being examined with 0.01M *hydrochloric acid* to obtain a 0.08% w/v solution. Add 4 µL of *6M hydrochloric acid* per mL of this solution. Maintain the solution at 2° to 8° and use within 48 hours.

(2) Dissolve the contents of a vial of *insulin lispro EPCRS* in 0.01M *hydrochloric acid* to obtain a solution containing 0.08% w/v insulin lispro. Maintain the solution at 2° to 8° and use within 48 hours.

(3) Prepare a 0.1% w/v solution of the preparation being examined in 0.01M *hydrochloric acid* and add 4 µL of *6M hydrochloric acid* per mL and allow to stand at room temperature (generation of A21 desamido insulin lispro) Store the solution at 2° to 8° and use within 14 days.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mix 255 volumes of *acetonitrile for chromatography* and 745 volumes of a 2.84% w/v solution of *anhydrous sodium sulfate* adjusted to pH 2.3 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of insulin lispro is about 24 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to insulin lispro and A21 desamido insulin lispro is at least 1.8 and the maximum relative standard deviation for three replicate injections is not greater than 1.1%.

DETERMINATION OF CONTENT

Calculate the content of insulin lispro, $C_{257}H_{383}N_{65}O_{77}S_6$, from the chromatograms obtained and using the declared content of $C_{257}H_{383}N_{65}O_{77}S_6$ in *insulin lispro EPCRS*.

For soluble insulin lispro

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A A solution containing 0.708% w/v of *tris(hydroxymethyl)aminomethane hydrochloride* and 0.668% w/v of *tris(hydroxymethyl)aminomethane* in *water*. (The pH of the final solution should be between 8.15 and 8.35).

(1) Dilute 1 volume of the preparation being examined with 1 volume of solution A and immerse in a water bath at 25°for 30 minutes. Filter the solution with a 0.2-µm low protein binding filter. Dilute 2 volumes of the filtrate with 1 volume of 0.2M *hydrochloric acid* and 2 volumes of 0.01M *hydrochloric acid*.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dissolve the contents of a vial of *insulin lispro EPCRS* in 0.01M *hydrochloric acid* to obtain a 0.08% w/v solution. Maintain the solution at 2° to 8° and use within 48 hours.

(3) Prepare a 0.1% w/v solution of the preparation being examined in 0.01M *hydrochloric acid* and add 4 µL of *6M hydrochloric acid* per mL and allow to stand at room temperature (generation of A21 desamido insulin lispro). Store the solution at 2° to 8° and use within 14 days.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay for insulin lispro may be used.

When the chromatograms are recorded under the prescribed conditions, the retention time of insulin lispro is about 24 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to insulin lispro and desamido insulin lispro, is at least 1.8 and the relative standard deviation for three replicate injections is not greater than 1.1%.

DETERMINATION OF CONTENT

Calculate the content of insulin lispro in solution from the chromatograms obtained and the declared content of $C_{257}H_{383}N_{65}O_{77}S_6$ in *insulin lispro EPCRS*.

LABELLING

The label states: (1) the ratio of soluble insulin lispro to insulin lispro protamine suspension used in the manufacturing process of biphasic insulin lispro injection; (2) the potency in units per mL.

100 units are equivalent to 3.47 mg of insulin lispro.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Biphasic Isophane Insulin Injection

General Notices

Biphasic Isophane Insulin

(Ph. Eur. monograph 0832

Action and use

Hormone; treatment of diabetes mellitus.

Ph Eur

Biphasic isophane insulin injection complies with the monograph on Insulin preparations, injectable (0854) with the exception of the test for Insulin in the supernatant and with the amendments prescribed below for the other tests.

DEFINITION

Biphasic isophane insulin injection is a sterile buffered suspension of either porcine or human insulin, complexed with protamine sulfate or another suitable protamine, in a solution of insulin of the same species.

PRODUCTION

Biphasic isophane insulin injection is prepared by carrying out the procedures described in the monograph on *Insulin preparations, injectable (0854)*.

Biphasic isophane insulin injection is produced by mixing, in defined ratios, soluble insulin injection and isophane insulin injection. The defined ratios shall be demonstrated by a test method which has been approved by the competent authority to comply with the label claim.

CHARACTERS

A white or almost white suspension which on standing deposits a white or almost white sediment and leaves a colourless or almost colourless supernatant; the sediment is readily resuspended by gently shaking. When examined under a microscope, the particles are seen to be rod-shaped crystals, the majority with a maximum dimension greater than 1 µm but rarely exceeding 60 µm, free from large aggregates.

IDENTIFICATION

Examine the chromatograms obtained in the Assay. The position of the peak due to insulin in the chromatogram obtained with the test solution corresponds to that of the principal peak obtained with the appropriate reference solution.

TESTS

www.webofpharma.com

https://thuvienthuocngocanh.com/

Total zinc

Not more than 40.0 µg per 100 IU of insulin, determined as described in the monograph on *Insulin preparations, injectable (0854)*.

LABELLING

The label states in addition to the indications mentioned in the monograph on *Insulin preparations, injectable (0854)* the ratio of soluble insulin injection to isophane insulin injection used in the manufacturing process of biphasic isophane insulin injection.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

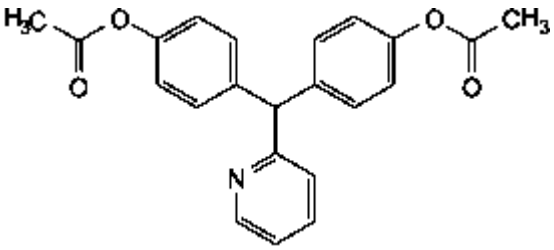
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bisacodyl

General Notices

(Ph. Eur. monograph 0595)



$C_{22}H_{19}NO_4$ 361.4 *603-50-9*

Action and use

Stimulant laxative.

Preparations

Bisacodyl Suppositories

Bisacodyl Gastro-resistant Tablets

Ph Eur

DEFINITION

[(Pyridin-2-yl)methylene]di(4,1-phenylene) diacetate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute mineral acids.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (2.2.14): 131 °C to 135 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison bisacodyl CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in chloroform R, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in acetone R and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of bisacodyl CRS in acetone R and dilute to 10 mL with the same solvent.

Plate TLC silica gel GF_{254} plate R.

Mobile phase methyl ethyl ketone R, xylene R (50:50 *V/V*).

Application 10 µL.

Development Over a path of 10 cm.

Drying In air, if necessary heating at 100-105 °C.

Detection Spray with a mixture of equal volumes of 0.05 M iodine and dilute sulfuric acid R.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Acidity or alkalinity

To 1.0 g add 20 mL of carbon dioxide-free water R, shake, heat to boiling, cool and filter. Add 0.2 mL of 0.01 M sodium hydroxide and 0.1 mL of methyl red solution R. The solution is yellow. Not more than 0.4 mL of 0.01 M hydrochloric acid is required to change the colour of the indicator to red.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture glacial acetic acid R, acetonitrile R, water R (4:30:66 *V/V/V*).

Test solution Dissolve 50 mg of the substance to be examined in 25 mL of acetonitrile R and dilute to 50.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2 mg of *bisacodyl for system suitability A CRS* (containing impurities A, B, C and E) in 1 mL of *acetonitrile R* and dilute to 2 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *bisacodyl for peak identification CRS* (containing impurity F) in 2.5 mL of *acetonitrile R* and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 45 volumes of *acetonitrile R* and 55 volumes of a 1.58 g/L solution of *ammonium formate R* previously adjusted to pH 5.0 with *anhydrous formic acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL.

Run time 3.5 times the retention time of bisacodyl.

Identification of impurities Use the chromatogram supplied with *bisacodyl for system suitability A CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity F.

Relative retention With reference to bisacodyl (retention time = about 13 min): impurity A = about 0.2; impurity B = about 0.4; impurity C = about 0.45; impurity E = about 0.9; impurity F = about 2.6.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to bisacodyl.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.7;

— *impurities C, E*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity F*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (2.2.20).

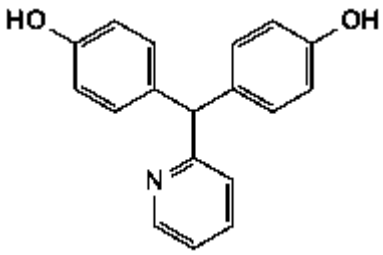
1 mL of *0.1 M perchloric acid* is equivalent to 36.14 mg of $C_{22}H_{19}NO_4$.

STORAGE

Protected from light.

IMPURITIES

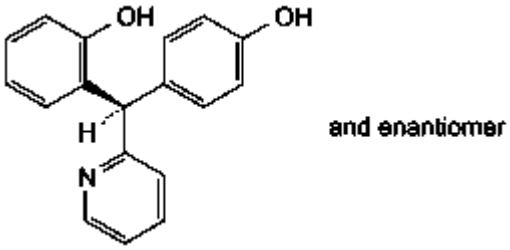
Specified impurities *A, B, C, E, F.*



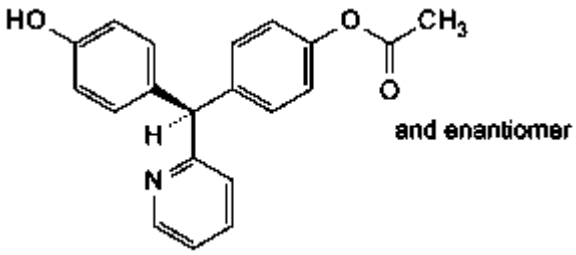
A. 4,4′-[(pyridin-2-yl)methylene]diphenol,

www.webofpharma.com

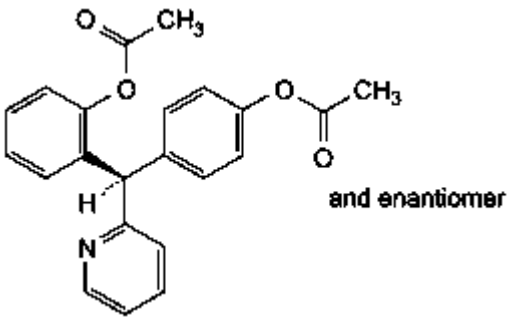
https://thuocngocanh.com/



B. 2-[(*RS*)-(4-hydroxyphenyl)(pyridin-2-yl)methyl]phenol,



C. 4-[(*RS*)-(4-hydroxyphenyl)(pyridin-2-yl)methyl]phenyl acetate,



E. 2-[(*RS*)-[4-(acetyloxy)phenyl](pyridin-2-yl)methyl]phenyl acetate,

F. unknown structure.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bisacodyl Gastro-resistant Tablets

General Notices

Bisacodyl Tablets

Gastro-resistant Bisacodyl Tablets

Action and use

Stimulant laxative.

DEFINITION

Bisacodyl Gastro-resistant Tablets contain Bisacodyl. They are made gastro-resistant by enteric coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bisacodyl, $C_{22}H_{19}NO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

B. Extract a quantity of the powdered tablets containing 50 mg of Bisacodyl with 20 mL of *dichloromethane*, filter, evaporate the filtrate to dryness and dissolve the residue in 10 mL of a 0.5% v/v solution of *sulfuric acid*. To 2 mL of the solution obtained add *sulfuric acid*. A reddish violet colour is produced on addition of the concentrated acid.

C. Boil 2 mL of the solution obtained in test B with a little *nitric acid*; a yellow colour is produced. Cool and add 5M *sodium hydroxide*; the colour becomes yellowish brown.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

First stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 500 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 2 hours, withdraw a 10-mL sample of the medium.

(2) Dissolve 50 mg of *bisacodyl BPCRS* in 50 mL of *methanol* containing a drop of *orthophosphoric acid*. Dilute with *0.1M hydrochloric acid* to produce a solution containing 0.00005% w/v of *bisacodyl BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

350 volumes of a 0.1% w/v solution of *ammonium acetate*, adjusted to pH 8.0 with *dilute ammonia solution* and 650 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of $C_{22}H_{19}NO_4$ in the medium using the declared content of $C_{22}H_{19}NO_4$ in *bisacodyl BPCRS*.

LIMITS

The amount of bisacodyl released is not more than 5% of the stated amount.

After completion of the first stage, remove the basket from the vessel and dip once into a 100-mL beaker containing 80 mL of *water*. After the water has drained from the basket, transfer the tablet to Apparatus 2 and carry out the procedure described under Final stage.

Final stage

Solution A: Dissolve 8.9 g of *disodium hydrogen orthophosphate* and 10 g of *sodium lauryl sulfate* in 800 mL of *water*. Adjust to pH 7.5 with 0.1M *hydrochloric acid* and dilute to 1000 mL with *water*.

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 60 minutes, withdraw a 10-mL sample of the medium and filter through a 0.45-µm filter, discarding the first 3 mL. Use the filtered medium, diluted with dissolution medium, if necessary, to produce a solution expected to contain 0.00056% w/v of bisacodyl.

(2) Dissolve 50 mg of *bisacodyl BPCRS* in 50 mL of *methanol* containing a drop of *orthophosphoric acid*. Dilute with solution A to produce a solution containing 0.00056% w/v of *bisacodyl BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution – First stage may be used.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of $C_{22}H_{19}NO_4$ in the medium using the declared content of $C_{22}H_{19}NO_4$ in *bisacodyl BPCRS*.

LIMITS

The amount of bisacodyl released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B: A mixture of 4 volumes of *glacial acetic acid*, 30 volumes of *acetonitrile* and 66 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing 25 mg of Bisacodyl with 40 mL of solution B, dilute to 50 mL with solution B and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution B.

(3) Dissolve the contents of a vial of *bisacodyl for system suitability A EPCRS* in 1 mL of *acetonitrile* and mix with 1 mL of solution B.

(4) Dissolve 5 mg of *bisacodyl for peak identification EPCRS* in 2.5 mL of *acetonitrile* and dilute to 5 mL with solution B.

(5) Dilute 1 volume of solution (2) to 10 volumes with solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3.5 times the retention time of the principal peak.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of 0.025M *ammonium formate* previously adjusted to pH 5.0 with *anhydrous formic acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to bisacodyl (retention time about 13 minutes) are: impurity A, about 0.2; impurity B, about 0.4; impurity C, about 0.45; impurity E, about 0.9; impurity F, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.5, where H_p is the height above the baseline of the peak due to impurity E and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bisacodyl.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

identify any peak corresponding to impurity A using solution (3) and multiply the area of this peak by a correction factor of 0.7;

the area of any peak corresponding to impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

the area of any peak corresponding to impurity E is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity F is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B: A mixture of 4 volumes of *glacial acetic acid*, 30 volumes of *acetonitrile* and 66 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing 10 mg of Bisacodyl with 40 mL of solution B, dilute to 50 mL and filter. Further dilute 1 volume to 4 volumes with solution B.
(2) 0.005% w/v of *bisacodyl BPCRS* in solution B.
(3) Dissolve the contents of a vial of *bisacodyl for system suitability A EPCRS* in 1 mL of *acetonitrile* and mix with 1 mL of solution B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used, with the exception of run time.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.5, where H_p is the height above the baseline of the peak due to impurity E and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bisacodyl.

DETERMINATION OF CONTENT

Calculate the total content of bisacodyl, $C_{22}H_{19}NO_4$, in the tablets using the chromatograms obtained and the declared content of $C_{22}H_{19}NO_4$ in *bisacodyl BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Bisacodyl.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bisacodyl Suppositories

General Notices

Action and use

Stimulant laxative.

DEFINITION

Bisacodyl Suppositories contain Bisacodyl in a suitable suppository basis.

The suppositories comply with the requirements stated under Rectal Preparations and with the following requirements.

Content of bisacodyl, $C_{22}H_{19}NO_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method described under Related substances applying to the plate 2 µL of each solution and using as solution (2) a 1% w/v solution of *bisacodyl BPCRS* in *acetone*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Dissolve a quantity of the suppositories containing 0.15 g of Bisacodyl as completely as possible in 150 mL of *petroleum spirit (boiling range, 40° to 60°)*, filter, wash the residue with *petroleum spirit (boiling range, 40° to 60°)* until free from fatty material and dry at about 100°. Wash with a very small quantity of warm *chloroform* and dissolve the residue in 10 mL of a 0.5% v/v solution of *sulfuric acid*. To 2 mL of the solution add 0.05 mL of *potassium tetraiodomercurate solution*. A white precipitate is produced.

C. To 2 mL of the solution obtained in test B add *sulfuric acid*. A reddish violet colour is produced.

D. Boil 2 mL of the solution obtained in test B with a little *nitric acid*; a yellow colour is produced. Cool and add 5M *sodium hydroxide*; the colour becomes yellowish brown.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of equal volumes of *butan-2-one* and *xylene* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) shake a quantity of the suppositories containing 20 mg of Bisacodyl with 20 mL of *petroleum spirit (boiling range, 40° to 60°)*, filter, wash the residue with *petroleum spirit (boiling range, 40° to 60°)* until free from fat and dissolve in 2 mL of *acetone*. For solution (2) dilute 3 volumes of solution (1) to 100 volumes with *acetone*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

To a quantity of the suppositories containing 0.1 g of Bisacodyl add 80 mL of *anhydrous acetic acid* previously neutralised with *0.02M perchloric acid VS* to *1-naphthol-benzein solution*, warm gently until solution is complete and immediately carry out Method I for *non-aqueous titration*, Appendix VIII A, using *0.02M perchloric acid VS* and determining the end point potentiometrically. Each mL of *0.02M perchloric acid VS* is equivalent to 7.228 mg of $C_{22}H_{19}NO_4$. Calculate the average content of bisacodyl, $C_{22}H_{19}NO_4$, in the suppositories.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bismuth Subcarbonate

General Notices

Bismuth Carbonate

(Ph. Eur. monograph 0012)

Ph Eur

DEFINITION

Content

80.0 per cent to 82.5 per cent of Bi (A_r 209.0) (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves with effervescence in mineral acids.

IDENTIFICATION

A. It gives the reaction of carbonates (*2.3.1*).

B. It gives the reactions of bismuth (*2.3.1*).

TESTS

Solution S

Shake 5.0 g with 10 mL of *water R* and add 20 mL of *nitric acid R*. Heat to dissolve, cool and dilute to 100 mL with *water R*.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

Chlorides (*2.4.4*)

Maximum 500 ppm.

www.webofpharma.com

https://thuvienthuocngocanh.com/

To 6.6 mL of solution S add 4 mL of *nitric acid R* and dilute to 50 mL with *water R*.

Nitrates

Maximum 0.4 per cent.

To 0.25 g in a 125 mL conical flask, add 20 mL of *water R*, 0.05 mL of *indigo carmine solution R1* and then, as a single addition but with caution, 30 mL of *sulfuric acid R*. Titrate immediately with *indigo carmine solution R1* until a stable blue colour is obtained. Not more than *n* mL of the titrant is required, *n* being the volume corresponding to 1 mg of NO_3.

Alkali and alkaline-earth metals

Maximum 1.0 per cent.

To 1.0 g add 10 mL of *water R* and 10 mL of *acetic acid R*. Boil for 2 min, cool and filter. Wash the residue with 20 mL of *water R*. To the combined filtrate and washings add 2 mL of *dilute hydrochloric acid R* and 20 mL of *water R*. Boil and pass *hydrogen sulfide R* through the boiling solution until no further precipitate is formed. Filter, wash the residue with *water R*, evaporate the combined filtrate and washings to dryness on a water-bath and add 0.5 mL of *sulfuric acid R*. Ignite gently and allow to cool. The residue weighs a maximum of 10 mg.

Arsenic (*2.4.2, Method A*)

Maximum 5 ppm.

To 0.5 g in a distillation flask add 5 mL of *water R* and 7 mL of *sulfuric acid R*, allow to cool and add 5 g of *reducing mixture R* and 10 mL of *hydrochloric acid R*. Heat the contents of the flask to boiling gradually over 15-30 min and continue heating at such a rate that the distillation proceeds steadily until the volume in the flask is reduced by half or until 5 min after the air-condenser has become full of steam. It is important that distillation be discontinued before fumes of sulfur trioxide appear. Collect the distillate in a tube containing 15 mL of *water R* cooled in ice-water. Wash down the condenser with *water R* and dilute the distillate to 25 mL with the same solvent. Prepare the standard using a mixture of 2.5 mL of *arsenic standard solution (1 ppm As) R* and 22.5 mL of *water R*.

Copper

Maximum 50 ppm.

To 5 mL of solution S, add 2 mL of *ammonia R* and dilute to 50 mL with *water R*. Filter. To 10 mL of the filtrate add 1 mL of a 1 g/L solution of *sodium diethyldithiocarbamate R*. The solution is not more intensely coloured than a standard prepared at the same time in the same manner using a mixture of 0.25 mL of *copper standard solution (10 ppm Cu) R* and 9.75 mL of *water R* instead of 10 mL of the filtrate.

Lead

Maximum 20 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Dissolve 12.5 g in 75 mL of a mixture of equal volumes of *lead-free nitric acid R* and *water R*. Boil for 1 min, cool and dilute to 100.0 mL with *water R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions Prepare the reference solutions using appropriate quantities of lead standard solution and a 37 per cent *V/V* solution of *lead-free nitric acid R*.

Source Lead hollow-cathode lamp.

Wavelength 283.3 nm (depending on the apparatus, the line at 217.0 nm may be used).

Atomisation device Air-acetylene flame.

Silver

Maximum 25 ppm.

To 2.0 g add 1 mL of *water R* and 4 mL of *nitric acid R*. Heat gently until dissolved and dilute to 11 mL with *water R*. Cool and add 2 mL of *1 M hydrochloric acid*. Allow to stand protected from light for 5 min. Any opalescence in the solution is not more intense than that in a standard prepared at the same time in the same manner using a mixture of 10 mL of *silver standard solution (5 ppm Ag) R*, 1 mL of *nitric acid R* and 2 mL of *1 M hydrochloric acid*.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.500 g in 3 mL of *nitric acid R* and dilute to 250 mL with *water R*. Carry out the complexometric titration of bismuth (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 20.90 mg of Bi.

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

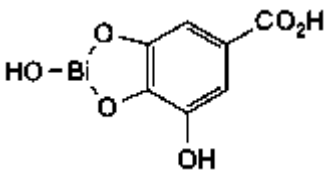
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bismuth Subgallate

General Notices

(Ph. Eur. monograph 1493)



$C_7H_5BiO_6$ 394.1 *99-26-3*

Ph Eur

DEFINITION

Complex of bismuth and gallic acid.

Content

48.0 per cent to 51.0 per cent of Bi (A_r 209.0) (dried substance).

CHARACTERS

Appearance

Yellow powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in mineral acids with decomposition and in solutions of alkali hydroxides, producing a reddish-brown liquid.

IDENTIFICATION

A. Mix 0.1 g with 5 mL of *water R* and 0.1 mL of *phosphoric acid R*. Heat to boiling and maintain boiling for 2 min. Cool and filter. To the filtrate, add 1.5 mL of *ferric chloride solution R1*; a blackish-blue colour develops.

B. It gives reaction (b) of bismuth (2.3.1).

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

In a porcelain or quartz dish, ignite 1.0 g, increasing the temperature very gradually. Heat in a muffle furnace at 600 ± 50 °C for 2 h. Cool and dissolve the residue with warming in 4 mL of a mixture of equal volumes of *lead-free nitric acid R* and *water R* and dilute to 20 mL with *water R*.

Acidity

Shake 1.0 g with 20 mL of *water R* for 1 min and filter. To the filtrate add 0.1 mL of *methyl red solution R*. Not more than 0.15 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Chlorides (*2.4.4*)

Maximum 200 ppm.

To 0.5 g add 10 mL of *dilute nitric acid R*. Heat on a water-bath for 5 min and filter. Dilute 5 mL of the filtrate to 15 mL with *water R*.

Nitrates

Maximum 0.2 per cent.

To 1.0 g add 25 mL of *water R* then 25 mL of a mixture of 2 volumes of *sulfuric acid R* and 9 volumes of *water R*. Heat at about 50 °C for 1 min with stirring and filter. To 10 mL of the filtrate, carefully add 30 mL of *sulfuric acid R*. The solution is not more intensely brownish-yellow than a reference solution prepared at the same time as follows: to 0.4 g of *gallic acid R*, add 20 mL of *nitrate standard solution (100 ppm NO_3) R* and 30 mL of a mixture of 2 volumes of *sulfuric acid R* and 9 volumes of *water R*, then filter; to 10 mL of the filtrate, carefully add 30 mL of *sulfuric acid R*.

Copper

Maximum 50 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Solution S.

Reference solutions Prepare the reference solutions using *copper standard solution (10 ppm Cu) R* and diluting with a 6.5 per cent *V/V* solution of *lead-free nitric acid R*.

Source Copper hollow-cathode lamp.

Wavelength 324.7 nm.

Atomisation device Air-acetylene flame.

Lead

Maximum 20 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Solution S.

Reference solutions Prepare the reference solutions using *lead standard solution (10 ppm Pb) R* and diluting with a 6.5 per cent *V/V* solution of *lead-free nitric acid R*.

Source Lead hollow-cathode lamp.

Wavelength 283.3 nm (depending on the apparatus, the line at 217.0 nm may be used).

Atomisation device Air-acetylene flame.

Silver

Maximum 25 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Solution S.

Reference solutions Prepare the reference solutions using *silver standard solution (5 ppm Ag) R* and diluting with a 6.5 per cent *V/V* solution of *lead-free nitric acid R*.

Source Silver hollow-cathode lamp.

Wavelength 328.1 nm.

Atomisation device Air-acetylene flame.

Substances not precipitated by ammonia

Maximum 1.0 per cent.

In a porcelain or quartz dish, ignite 2.0 g, increasing the temperature very gradually to 600 ± 50 °C; allow to cool. Moisten the residue with 2 mL of *nitric acid R*, evaporate to dryness on a water-bath and carefully heat and ignite once more at 600 ± 50 °C. After cooling, dissolve the residue in 5 mL of *nitric acid R* and dilute to 20 mL with *water R*. To 10 mL of this solution, add *concentrated ammonia R* until alkaline and filter. Wash the residue with *water R* and evaporate the combined filtrate and washings to dryness on a water-bath. Add 0.3 mL of *dilute sulfuric acid R* and ignite. The residue weighs a maximum of 10 mg.

Loss on drying (*2.2.32*)

Maximum 7.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

To 0.300 g add 10 mL of a mixture of equal volumes of *nitric acid R* and *water R*, heat to boiling and maintain boiling for 2 min. Add 0.1 g of *potassium chlorate R*, heat to boiling and maintain boiling for 1 min. Add 10 mL of *water R* and heat until the solution becomes colourless. To the hot solution, add 200 mL of *water R* and 50 mg of *xylenol orange triturate R*. Titrate with *0.1 M sodium edetate* until a yellow colour is obtained.

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *0.1 M sodium edetate* is equivalent to 20.90 mg of Bi.

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Bismuth Subsalicylate

General Notices

(Ph. Eur. monograph 1495)

$C_7H_5BiO_4$ 362.1 *14882-18-9*

Ph Eur

DEFINITION

Complex of bismuth and salicylic acid.

Content

56.0 per cent to 59.4 per cent of Bi (A_r 209.0) (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in mineral acids with decomposition.

IDENTIFICATION

A. To 0.5 g add 10 mL of *hydrochloric acid R1*. Heat on a water-bath for 5 min. Cool and filter. Retain the filtrate for identification test B. Wash the residue with *dilute hydrochloric acid R* and then with *water R*. Dissolve the residue in 0.5-1 mL of *dilute sodium hydroxide solution R*. Add 15 mL of *water R*. Neutralise with *dilute hydrochloric acid R*. The solution gives reaction (a) of salicylates (*2.3.1*).

B. The filtrate obtained in identification test A gives reaction (b) of bismuth (*2.3.1*).

TESTS

Solution S

In a porcelain or quartz dish, ignite 1.0 g, increasing the temperature very gradually. Heat in a muffle furnace at 600 ± 25 °C for 2 h. Cool and dissolve the residue with warming in 4 mL of a mixture of equal volumes of *lead-free nitric acid R* and *water R* and dilute to 20 mL with

www.webofpharma.com

https://thuocngocanh.com/

water R.

Acidity

Shake 2.0 g with 30 mL of *ether R* for 1 min and filter. To the filtrate add 30 mL of *alcohol R* and 0.1 mL of *thymol blue solution R*. Not more than 0.35 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dissolve 0.250 g in a mixture of 2 mL of *nitric acid R*, 5 mL of *water R* and 8 mL of *methanol R*.

Nitrates

Maximum 0.4 per cent.

To 0.1 g add 10 mL of *water R* and, with caution, 20 mL of *sulfuric acid R* and stir. The solution is not more intensely yellow coloured than a reference solution prepared at the same time using 0.1 g of *salicylic acid R*, 6 mL of *water R*, 4 mL of *nitrate standard solution (100 ppm NO_3) R* and 20 mL of *sulfuric acid R*.

Copper

Maximum 50 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Solution S.

Reference solutions Prepare the reference solutions using *copper standard solution (10 ppm Cu) R* and diluting with a 6.5 per cent *V/V* solution of *lead-free nitric acid R*.

Source Copper hollow-cathode lamp.

Wavelength 324.7 nm.

Atomisation device Air-acetylene flame.

Lead

Maximum 20 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Solution S.

Reference solutions Prepare the reference solutions using *lead standard solution (10 ppm Pb) R* and diluting with a 6.5 per cent *V/V* solution of *lead-free nitric acid R*.

www.webofpharma.com

https://thuocngocanh.com/

Source Lead hollow-cathode lamp.

Wavelength 283.3 nm (depending on the apparatus, the line at 217.0 nm may be used).

Atomisation device Air-acetylene flame.

Silver

Maximum 25 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Solution S.

Reference solutions Prepare the reference solutions using *silver standard solution (5 ppm Ag) R* and diluting with a 6.5 per cent *V/V* solution of *lead-free nitric acid R*.

Source Silver hollow-cathode lamp.

Wavelength 328.1 nm.

Atomisation device Air-acetylene flame.

Soluble bismuth

Maximum 40 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Suspend 5.0 g in 100 mL of *water R*. Stir constantly for 2 h at 20-23 °C. Filter through filter paper (slow filtration) then through a cellulose micropore membrane filter (0.1 µm). To 10.0 mL of clear filtrate, add 0.1 mL of *nitric acid R*.

Reference solutions Prepare the reference solutions using *bismuth standard solution (100 ppm Bi) R* and diluting with a mixture of equal volumes of *dilute nitric acid R* and *water R*.

Source Bismuth hollow-cathode lamp.

Wavelength 223.06 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve with heating 0.300 g in 10 mL of a mixture of 2 volumes of *perchloric acid R* and 5 volumes of *water R*. To the hot solution, add 200 mL of *water R* and 50 mg of *xylenol orange triturate R*. Titrate with *0.1 M sodium edetate* until a yellow colour is obtained.

https://thuocngocanh.com/

1 mL of *0.1 M sodium edetate* is equivalent to 20.90 mg of Bi.

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

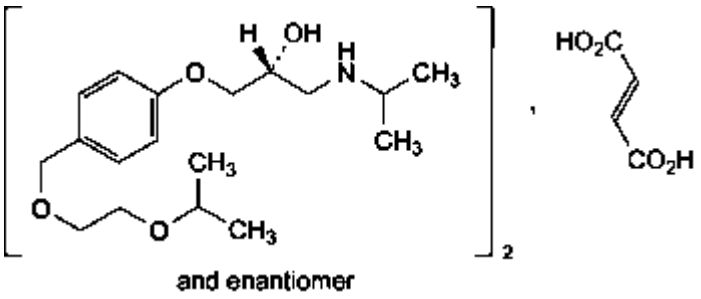
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bisoprolol Fumarate

General Notices

(Ph. Eur. monograph 1710)



and enantiomer

$C_{40}H_{66}N_2O_{12}$ 767 *104344-23-2*

Action and use

Beta-adrenoceptor antagonist.

Preparation

Bisoprolol Tablets

Ph Eur

DEFINITION

(2*RS*)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]propan-2-ol fumarate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder.

Solubility

Very soluble in water, freely soluble in methanol.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *bisoprolol fumarate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate and dry the residues at 60 °C at a pressure not exceeding 0.7 kPa and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R1*, *water for chromatography R* (20:80 *V/V*).

Test solution Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *bisoprolol for peak identification CRS* (containing impurities A and E) in 1.0 mL of the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *bisoprolol for system suitability CRS* (containing impurity G) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 20 ± 2 °C.

Mobile phase:

— *mobile phase A*: 10 g/L solution of *phosphoric acid R*;

— *mobile phase B*: 10 g/L solution of *phosphoric acid R* in *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	95	5
4 - 8	95 → 80	5 → 20

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
8 - 15	80	20
15 - 34	80 → 20	20 → 80
34 - 36	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *bisoprolol for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to fumaric acid and impurities A and E; use the chromatogram supplied with *bisoprolol for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity G.

Relative retention With reference to bisoprolol (retention time = about 18 min): impurity A = about 0.5; impurity G = about 1.1; impurity E = about 1.2.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to bisoprolol.

Limits:

— *impurity G*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to fumaric acid.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.000 g.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 38.35 mg of $C_{40}H_{66}N_2O_{12}$.

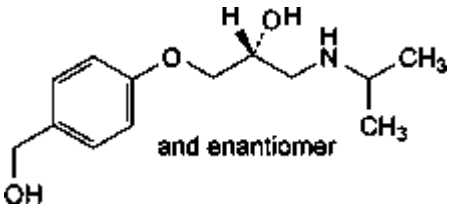
STORAGE

In an airtight container, protected from light.

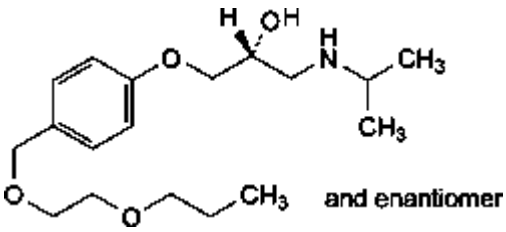
IMPURITIES

Specified impurities *A, E, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, F, K, L, N, Q, R, S, T, U.*



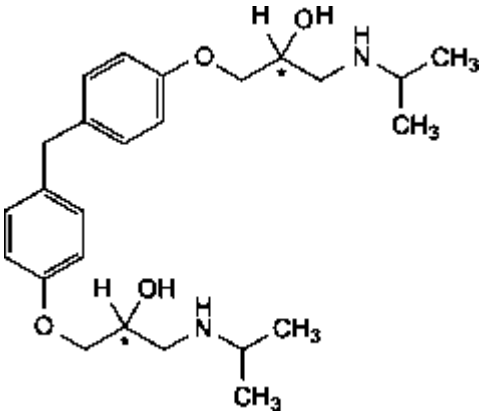
A. (2*RS*)-1-(4-hydroxymethyl-phenoxy)-3-isopropylaminopropan-2-ol,



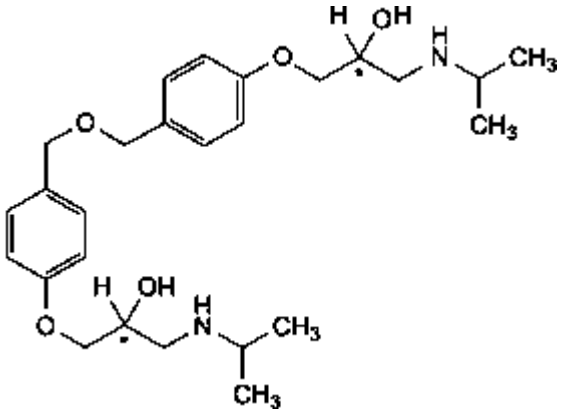
B. (2*RS*)-1-isopropylamino-3-[4-(2-propoxy-ethoxymethyl)phenoxy]propan-2-ol,

www.webofpharma.com

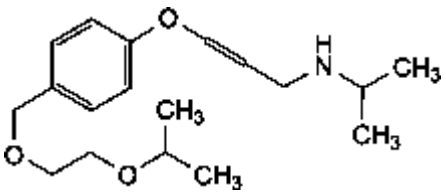
https://thuocngocanh.com/



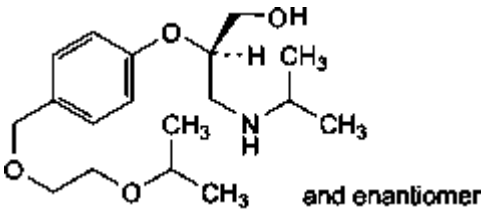
C. 1-[4-[4-(2-hydroxy-3-isopropylamino-propoxy)benzyl]phenoxy]-3-isopropylaminopropan-2-ol,



D. 1-[4-[4-(2-hydroxy-3-isopropylaminopropoxy)benzyloxylmethyl]phenoxy]-3-isopropylaminopropan-2-ol,



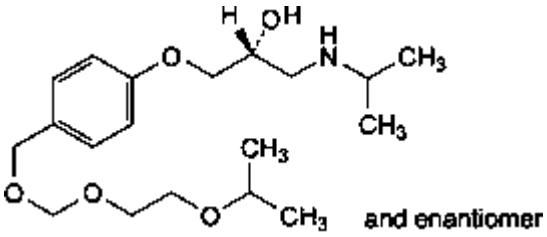
E. (*EZ*)-[3-[4-(2-isopropoxy-ethoxymethyl)phenoxy]allyl]isopropylamine,



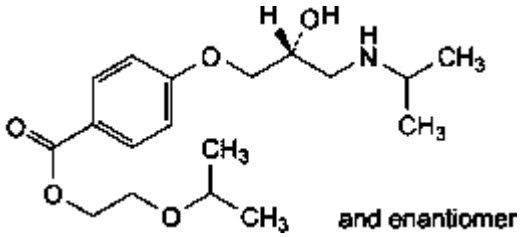
F. (2*RS*)-2-[4-(2-isopropoxy-ethoxymethyl)phenoxy]-3-isopropylaminopropan-2-ol,

www.webofpharma.com

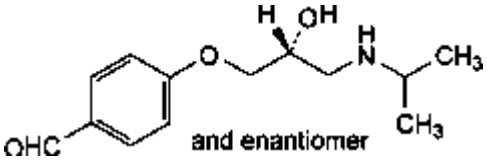
https://thuocngocanh.com/



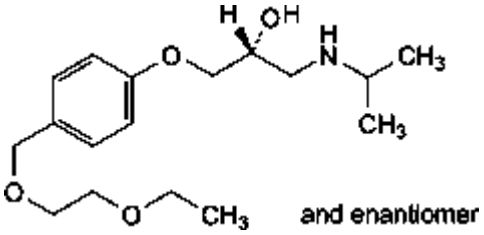
G. (2*RS*)-1-[4-[[(2-isopropoxyethoxy)methoxy]methyl]phenoxy]-3-isopropylaminopropan-2-ol,



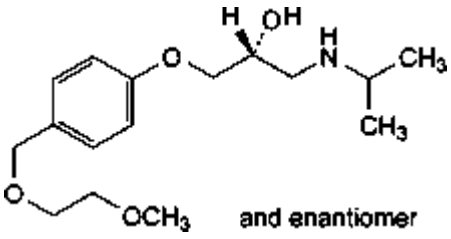
K. 2-isopropoxyethyl 4-[[(2*RS*)-2-hydroxy-3-(isopropylamino)propyl]oxy]benzoate,



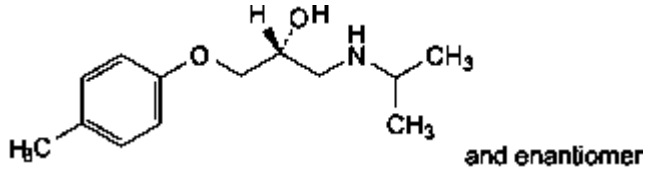
L. 4-[[(2*RS*)-2-hydroxy-3-(isopropylamino)propyl]oxy]benzaldehyde,



N. (2*RS*)-1-[4-[(2-ethoxyethoxy)methyl]phenoxy]-3-isopropylaminopropan-2-ol,



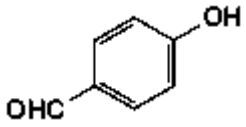
Q. (2*RS*)-1-(isopropylamino)-3-[4-(2-methoxyethoxy)methyl]phenoxypropan-2-ol,



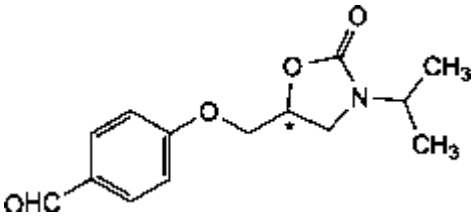
R. (2*RS*)-1-(isopropylamino)-3-(4-methylphenoxy)propan-2-ol,

www.webofpharma.com

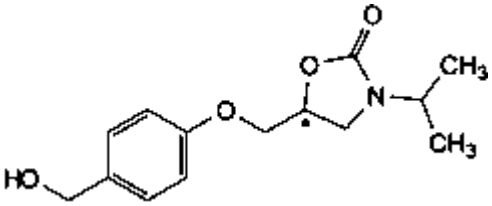
https://thuocngocanh.com/



S. 4-hydroxybenzaldehyde,



T. 4-[(3-isopropyl-2-oxo-1,3-oxazolidin-5-yl)methoxy]benzaldehyde,



U. 5-[[4-(hydroxymethyl)phenoxy]methyl]-3-isopropyl-1,3-oxazolidin-2-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bisoprolol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Bisoprolol Tablets contain Bisoprolol Fumarate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bisoprolol fumarate, $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the powdered tablets containing 10 mg of Bisoprolol Fumarate in *methanol*, dilute to 10 mL with the same solvent, mix and filter (a 0.45-µm nylon syringe filter is suitable).

(2) 0.1% w/v of *bisoprolol fumarate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below and allow to equilibrate for 1 hour.

(c) Apply 25 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *methanol* and 80 volumes of *ethyl acetate*. At the bottom of the chromatography tank, place a beaker containing 15 mL of *concentrated ammonia*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Solution A Prepare a solution containing 2.5 volumes of *orthophosphoric acid*, 5 volumes of *triethylamine*, 35 volumes of *water* and 160 volumes of *methanol*.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium, filter and dilute with sufficient of solution A to produce a solution expected to contain 0.0001% w/v of bisoprolol fumarate.

(2) 0.0002% w/v of *bisoprolol fumarate BPCRS* in *water*. Dilute 1 volume of this solution to 2 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (3.3 cm × 4.6 mm) packed with *octasilyl silica gel for chromatography* (3 µm) (Pecosphere 3CR C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 227 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

2 volumes of *triethylamine*, 68 volumes of *methanol* and 100 volumes of *water*, previously adjusted to pH 4.0 using *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of bisoprolol fumarate, $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$, in the medium from the chromatograms obtained and using the declared content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$, in *bisoprolol fumarate BPCRS*.

LIMITS

The amount of bisoprolol fumarate released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 2 volumes of *acetonitrile* and 8 volumes of *water*.

www.webofpharma.com

https://thietbiuocngocanh.com/

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 10 mg of Bisoprolol Fumarate. Add sufficient solvent to produce a 0.1% w/v solution of Bisoprolol Fumarate and filter (0.45-µm nylon syringe filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 5 volumes.

(4) Dissolve the contents of a vial of *bisoprolol for peak identification EPCRS* in 1.0 mL.

(5) Dissolve the contents of a vial of *bisoprolol for system suitability EPCRS* in 1.0 mL.

(6) Dilute 1 volume of *bisoprolol impurity standard BPCRS* to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Ace C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 20°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1% w/v solution of *orthophosphoric acid*.

Mobile phase B 1% w/v solution of *orthophosphoric acid* in *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	95	5	isocratic
4-8	95→80	5→20	linear gradient
8-15	80	20	isocratic
15-34	80→20	20→80	linear gradient
34-36	20	80	isocratic
36-37	20→95	80→5	linear gradient
37-46	95	5	re-equilibration

Use the chromatogram supplied with *bisoprolol for peak identification EPCRS* and the chromatogram obtained with solution (4) to identify the peaks due to fumaric acid and impurities A and E; use the chromatogram supplied with *bisoprolol for system suitability EPCRS* and the chromatogram obtained with solution (5) to identify the peak due to impurity G; use the chromatogram supplied with *bisoprolol impurity standard BPCRS* and the chromatogram obtained with solution (6) to identify the peaks due to impurities L, K and 1.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to bisoprolol (retention time about 22 minutes) are: impurity A, about 0.48; impurity L, about 0.55; impurity G, about 1.03; impurity K, about 1.05; impurity E, about 1.1; impurity 1, about 1.2 and impurity 2 (double peak), about 1.3.

www.webofpharma.com

https://thietbiuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 2.5, where H_p is the height above the baseline of the peak due to impurity G and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bisoprolol.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity K is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity L is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity 1 is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.6%);

the area of any peaks corresponding to impurity 2 or G are not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any *secondary peaks*, excluding the peaks due to impurity K and L, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%) and any peak due to fumaric acid.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Bisoprolol Fumarate comply with the requirement stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) To one tablet add 20 mL and mix with the aid of ultrasound. Dilute to produce a solution containing 0.005% w/v of Bisoprolol Fumarate and filter (0.45-µm nylon syringe filter is suitable).
(2) 0.005% w/v of *bisoprolol fumarate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thietbiuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (LiChrospher RP-Select B is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volume of *glacial acetic acid* and 1000 volumes of 0.136% *sodium acetate trihydrate* in *methanol (50%)*.

When the chromatograms are recorded under the prescribed conditions, the retention time of bisoprolol is about 5 minutes.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to bisoprolol is between 0.8 and 1.6.

DETERMINATION OF CONTENT

Calculate the content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ in each tablet using the declared content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ in *bisoprolol fumarate BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Bisoprolol Fumarate

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Bisoprolol Fumarate

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) To a quantity of the powdered tablets containing 25 mg of Bisoprolol Fumarate add 45 mL and mix with the aid of ultrasound. Dilute to produce a solution containing 0.005% w/v of Bisoprolol Fumarate and filter (a 0.45-µm nylon syringe filter is suitable).

(2) 0.005% w/v of *bisoprolol fumarate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

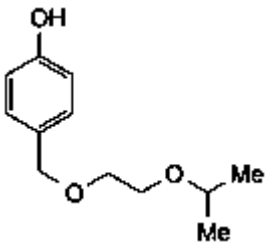
Calculate the content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ in the tablets using the declared content of $(C_{18}H_{31}NO_4)_2,C_4H_4O_4$ in *bisoprolol fumarate BPCRS*.

IMPURITIES

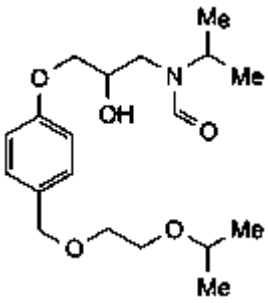
www.webofpharma.com

https://thietbiuocngocanh.com/

The impurities limited by the requirements of this monograph include those listed under Bisoprolol Fumarate and:



1. 4-{[2-(propan-2-yloxy)ethoxy]methyl}phenol



2. *rac*-*N*-(propan-2-yl)-*N*-{2-hydroxy-3-[(4-{[2-(propan-2-yloxy)ethoxy]methyl}phenyl)oxy]propyl}formamide (bisoprolol *N*-aldehyde)

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bleomycin Injection

General Notices

Bleomycin Sulphate for Injection

Action and use

Cytotoxic antibacterial.

DEFINITION

Bleomycin Injection is a sterile solution of Bleomycin Sulfate in a suitable liquid. It is prepared by dissolving Bleomycin Sulfate for Injection in the requisite amount of the liquid stated on the label before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Bleomycin Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

BLEOMYCIN SULFATE FOR INJECTION

DEFINITION

Bleomycin Sulfate for Injection is a sterile material consisting of Bleomycin Sulfate with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of bleomycin sulfate *(RS 367)*.

B. In the test for Composition, the retention time and size of the two principal peaks in the chromatogram obtained with solution (1) are approximately the same as those of the two principal peaks in the chromatogram obtained with solution (2).

C. Yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Acidity

www.webofpharma.com

https://thuocngocanh.com/

Dissolve a quantity in sufficient *carbon dioxide-free water* to produce a solution containing 10,000 IU of bleomycin per mL. The pH of the resulting solution is 4.5 to 6.0, Appendix V L.

Colour of solution

Dissolve a quantity in sufficient *water* to produce a solution containing 40,000 IU of bleomycin per mL. The *absorbance* of the solution at 430 nm is not greater than 0.15, Appendix II B.

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, lose not more than 6.0% of their weight. Use the combined contents of two containers.

Composition

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the contents of a sealed container in sufficient *water* to produce a solution containing 1000 IU of bleomycin per mL.
(2) 0.05% w/v of *bleomycin sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (7 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Use as the initial mobile phase a mixture of 10 volumes of *methanol* and 90 volumes of a mixture prepared in the following manner: dissolve 0.960 g of *sodium pentanesulfonate* in 900 mL of 0.08M *acetic acid*, add 1.86 g of *disodium edetate*, dilute to 1000 mL with 0.08M *acetic acid* and adjust to pH 4.3 with 18M *ammonia*. Maintain the initial mobile phase for 15 minutes, increase the proportion of *methanol* to 40 volumes over 60 minutes and maintain the final mobile phase until demethylbleomycin A_2 is eluted (about 20 minutes; retention time 1.5 to 2.5, relative to bleomycin A_2).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the two principal peaks is at least 5.

LIMITS

Using the chromatogram obtained with solution (1), calculate the percentage content of bleomycin components by *normalisation*. The proportions are within the following limits:

www.webofpharma.com

https://thietbiuocngocanh.com/

bleomycin A_2 (first principal peak), between 55% and 70%;

bleomycin B_2, between 25% and 32%;

the sum of the contents of bleomycin A_2 and bleomycin B_2 is not less than 85%;

demethylbleomycin A_2 (retention time 1.5 to 2.5, relative to bleomycin A_2), not greater than 8%;

the total content of other related substances is not greater than 9.5%.

Disregard any impurity present at less than 0.1%.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to produce a solution containing 15,000 IU of bleomycin per mL (solution A). The endotoxin limit concentration of solution A is 50 IU of endotoxin per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Mix the contents of the containers and carry out the *microbiological assay of antibiotics*, Appendix XIV A, Method A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

For a container of average content weight, the upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the stated number of IU.

STORAGE

The sealed container should be protected from light.

LABELLING

The label of the sealed container states the total number of IU (Units) contained in it.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

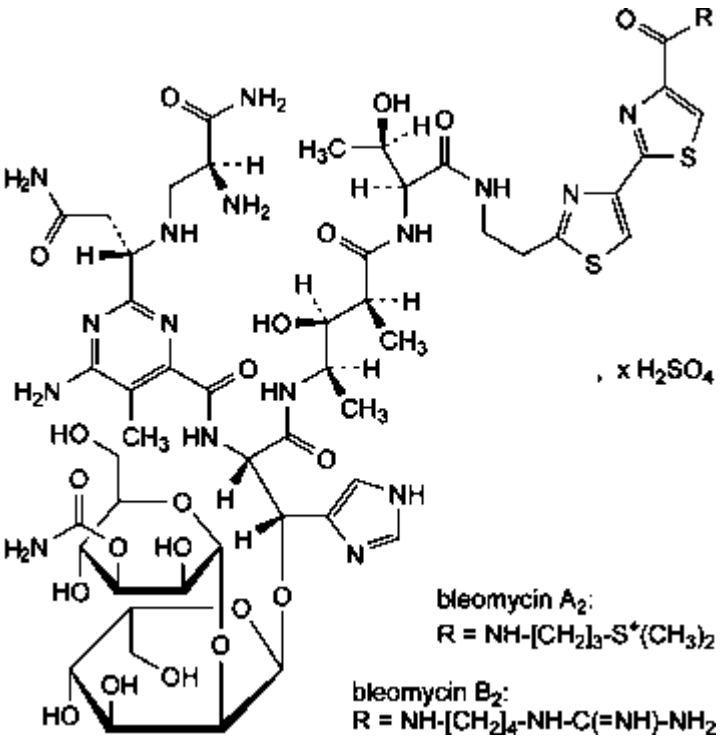
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bleomycin Sulfate

General Notices

Bleomycin Sulphate

(Ph. Eur. monograph 0976)



9041-93-4

Action and use

Cytotoxic antibacterial.

Preparation

Bleomycin Injection

Ph Eur

DEFINITION

Sulfate of a mixture of glycopeptides produced by *Streptomyces verticillus* or by any other means; the 2 principal components of the mixture are *N*-[3-(dimethylsulfaniumyl)propyl]bleomycinamide (bleomycin A_2) and *N*-[4-(carbamimidoylamino)butyl]bleomycinamide (bleomycin B_2).

www.webofpharma.com

https://thuocngocanh.com/

Potency

Minimum 1500 IU/mg (dried substance).

CHARACTERS

Appearance

White or yellowish-white, very hygroscopic powder.

Solubility

Very soluble in water, slightly soluble in anhydrous ethanol, practically insoluble in acetone.

IDENTIFICATION

A. Examine the chromatograms obtained in the test for composition.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time and size to the 2 principal peaks in the chromatogram obtained with reference solution (a).

B. It gives the reactions of sulfates (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 430 nm is not greater than 0.10.

Dissolve 0.200 g in *water R* and dilute to 10.0 mL with the same solvent.

pH (*2.2.3*)

4.5 to 6.0.

Dissolve 50 mg in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Composition

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *bleomycin sulfate CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.5 mL of reference solution (a) to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase:

— *mobile phase A*: *methanol R*;

— *mobile phase B*: dissolve 0.960 g of *sodium pentanesulfonate R* in 900 mL of acetic acid (4.8 g/L $C_2H_4O_2$), add 1.86 g of *sodium edetate R*, dilute to 1000 mL with the same solvent and adjust to pH 4.3 with *ammonia R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	10 → 40	90 → 60
60 - end	40	60

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time Until impurity D is eluted (about 80 min).

Relative retention With reference to bleomycin A_2: impurity D = 1.5 to 2.5.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to bleomycin A_2 (1^{st} principal peak) and bleomycin B_2 (2^{nd} principal peak) in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 20 for the principal peak in the chromatogram obtained with reference solution (b);

— *repeatability*: maximum relative standard deviation of 2 per cent for the principal peak after 6 injections of reference solution (a).

Limits:

— *bleomycin A_2*: 55 per cent to 70 per cent;

— *bleomycin B_2*: 25 per cent to 32 per cent;

— *sum of bleomycin A_2 and B_2*: minimum 85 per cent;

— *impurity D*: maximum 5.5 per cent;

— *sum of impurities other than D*: maximum 9.5 per cent;

— *disregard limit*: 0.1 per cent of the total.

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 50 mg by drying at 60 °C at a pressure not exceeding 0.67 kPa for 3 h.

Bacterial endotoxins (*2.6.14*)

Less than 5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*), using the diffusion method. Use *bleomycin sulfate CRS* as the chemical reference substance.

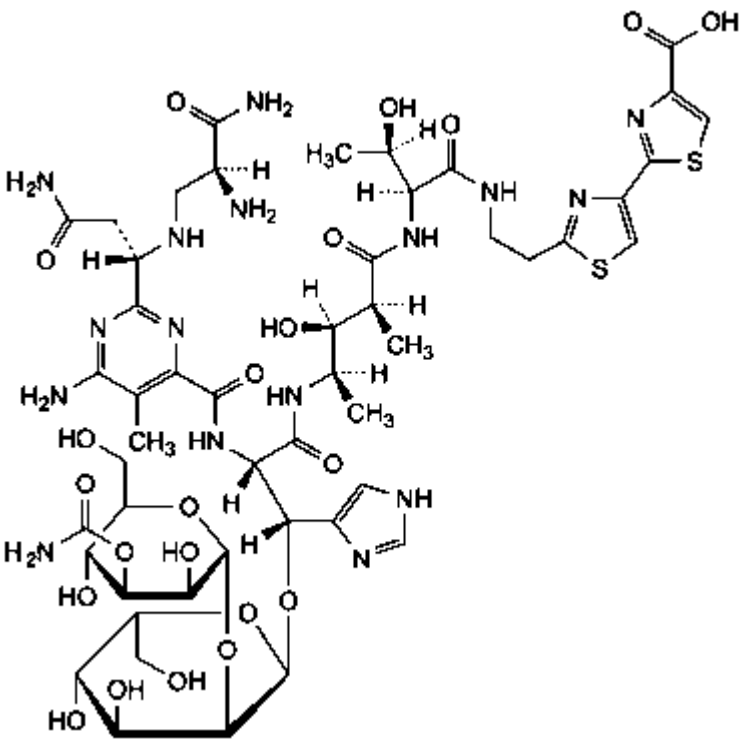
STORAGE

In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

Specified impurities D.

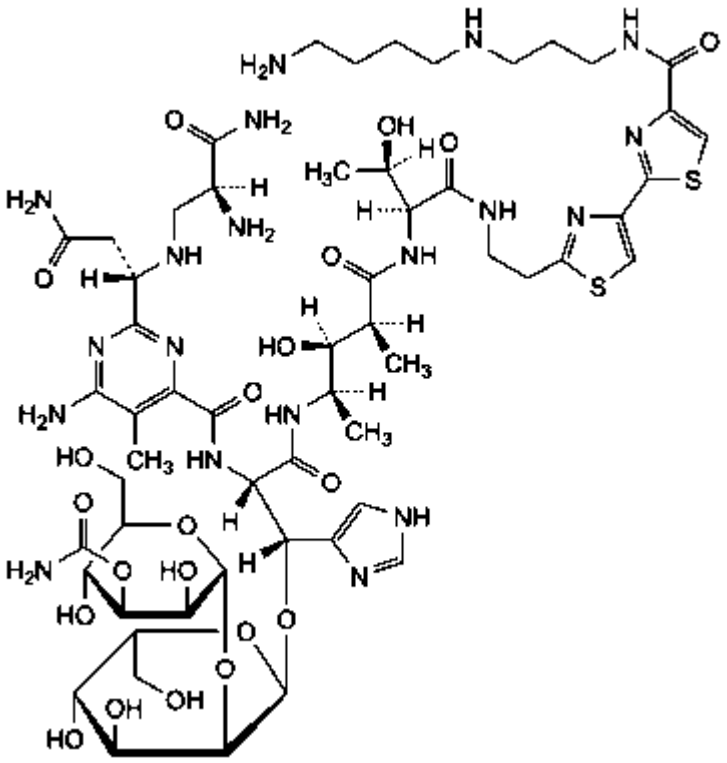
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.



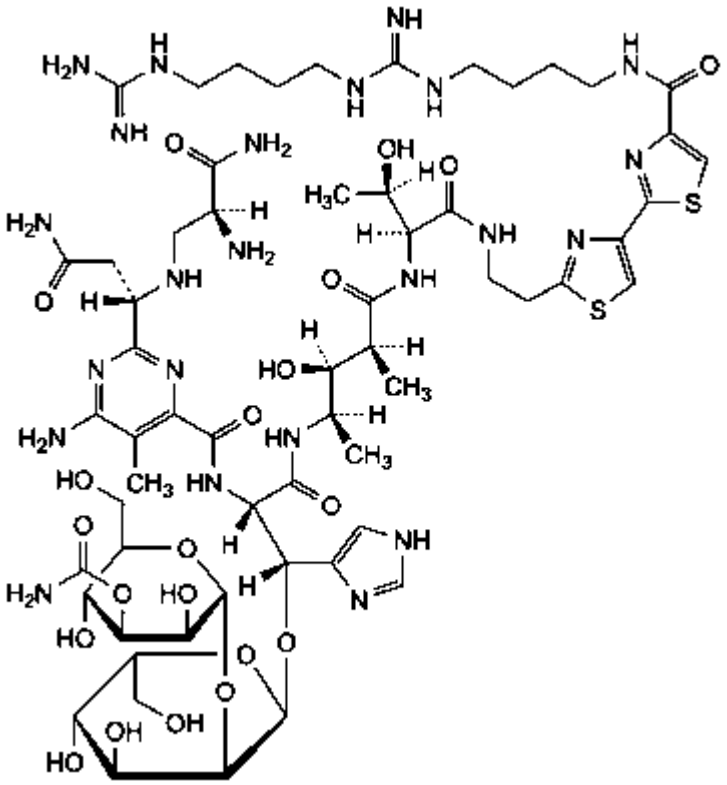
www.webofpharma.com

https://thuocngocanh.com/

A. bleomycinic acid,



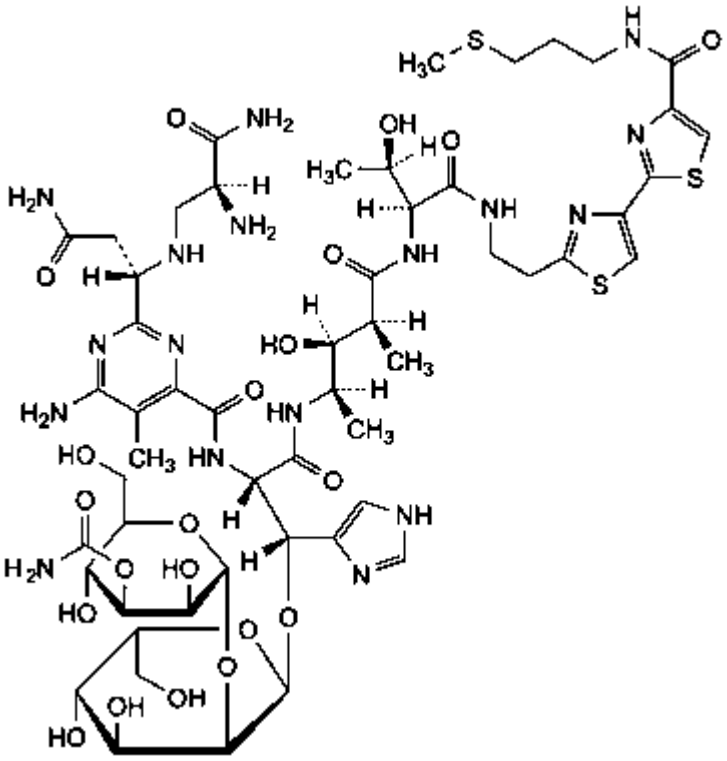
B. *N*-[3-[(4-aminobutyl)amino]propyl]bleomycinamide (bleomycin A_5),



C. *N*-[4-[[*N*-[4-(carbamimidoylamino)butyl]carbamimidoyl]amino]butyl]bleomycinamide (bleomycin B_4),

www.webofpharma.com

https://thuocngocanh.com/



D. *N*-[3-(methylsulfanyl)propyl]bleomycinamide (*S*-demethylbleomycin A_2).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

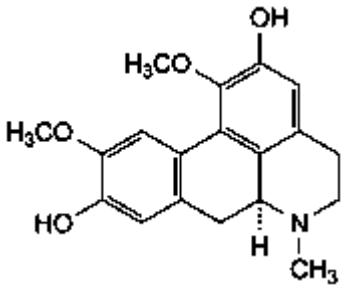
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Boldine

General Notices

(Ph. Eur. monograph 2971)



$C_{19}H_{21}NO_4$ 327.4 *476-70-0*

Action and use

Antioxidant.

Ph Eur

DEFINITION

(6a*S*)-1,10-Dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-2,9-diol, of vegetable origin.

Content

98.5 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white or yellowish, crystalline powder.

Solubility

Very slightly soluble in water, soluble in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute acid solutions.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *boldine CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 121.0 to + 127.0 (anhydrous substance).

Dissolve 0.500 g in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 12.0 mg of the substance to be examined in 8 mL of *methanol R* using sonication and dilute to 10.0 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 12 mg of *boldine for system suitability CRS* (containing impurities C and E) in 8 mL of *methanol R* using sonication and dilute to 10 mL with *methanol R*.

Reference solution (c) In order to prepare impurity A *in situ*, add 0.5 mL of *strong hydrogen peroxide solution R* to 5 mL of reference solution (b) and stir for 1 h.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.54 g of *ammonium acetate R* in 950 mL of *water for chromatography R*, adjust to pH 8.50 ± 0.05 with *diethylamine R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 38	85 → 64	15 → 36
38 - 50	64 → 20	36 → 80

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
50 - 53	20	80

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 302 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *boldine for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, C and E.

Relative retention With reference to boldine (retention time = about 23 min): impurity A = about 0.25; impurity C = about 0.6; impurity E = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 10.0 between the peaks due to impurity C and boldine.

Calculation of percentage contents:

— for each impurity, use the concentration of boldine in reference solution (a).

Limits:

— *impurity C*: maximum 1.5 per cent;

— *impurity A*: maximum 0.3 per cent;

— *impurity E*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent.

2-Propanol (*2.4.24*)

Maximum 1.0 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.100 g using the evaporation technique at 120 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

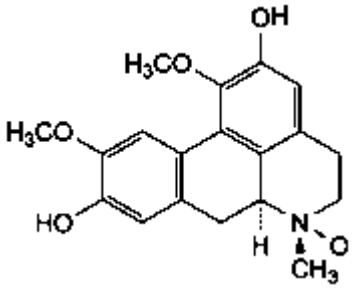
Dissolve 0.200 g in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 32.74 mg of $C_{19}H_{21}NO_4$.

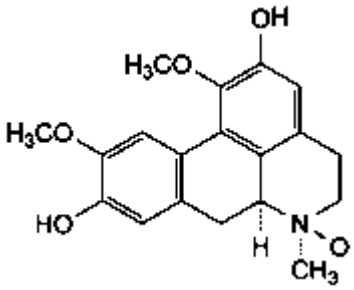
IMPURITIES

Specified impurities A, C, E.

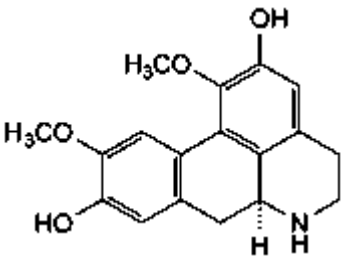
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, D.



A. (6*S*,6a*S*)-2,9-dihydroxy-1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline *N*-oxide,



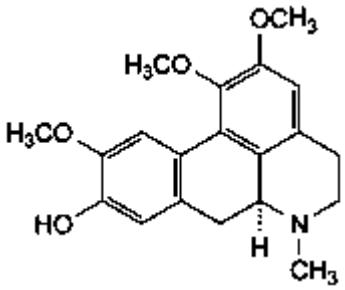
B. (6*R*,6a*S*)-2,9-dihydroxy-1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline *N*-oxide,



C. (6a*S*)-1,10-dimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline-2,9-diol,

www.webofpharma.com

https://thuocngocanh.com/



D. (6a*S*)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinolin-9-ol,

E. unknown structure.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Borax

General Notices

Sodium Borate

Sodium Tetraborate

(Ph. Eur. monograph 0013)

$Na_2B_4O_7,10H_2O$ 381.4 *1303-96-4*

Ph Eur

DEFINITION

Disodium tetraborate decahydrate.

Content

99.0 per cent to 103.0 per cent of $Na_2B_4O_7,10H_2O$.

CHARACTERS

Appearance

White or almost white, crystalline powder, colourless crystals or crystalline masses, efflorescent.

Solubility

Soluble in water, very soluble in boiling water, freely soluble in glycerol.

IDENTIFICATION

A. To 1 mL of solution S (see Tests) add 0.1 mL of *sulfuric acid R* and 5 mL of *methanol R* and ignite. The flame has a green border.

B. To 5 mL of solution S add 0.1 mL of *phenolphthalein solution R*. The solution is red. On the addition of 5 mL of *glycerol (85 per cent) R* the colour disappears.

C. Solution S gives the reactions of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 4.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

9.0 to 9.6 for solution S.

Sulfates (*2.4.13*)

Maximum 50 ppm, determined on solution S.

Use in this test 1.0 mL of *acetic acid R*. Prepare the standard using a mixture of 3 mL of *sulfate standard solution (10 ppm SO_4) R* and 12 mL of *distilled water R*.

Ammonium (*2.4.1*)

Maximum 10 ppm.

Dilute 6 mL of solution S to 14 mL with *water R*. Prepare the standard using a mixture of 2.5 mL of *ammonium standard solution (1 ppm NH_4) R* and 7.5 mL of *water R*.

Calcium (*2.4.3*)

Maximum 100 ppm, determined on solution S.

Prepare the standard using a mixture of 6 mL of *calcium standard solution (10 ppm Ca) R* and 9 mL of *distilled water R*.

ASSAY

Dissolve 20 g of *mannitol R* in 100 mL of *water R*, heating if necessary, cool and add 0.5 mL of *phenolphthalein solution R* and neutralise with *0.1 M sodium hydroxide* until a pink colour is obtained. Add 3.000 g of the substance to be examined, heat until dissolution is complete, cool, and titrate with *1 M sodium hydroxide* until the pink colour reappears.

1 mL of *1 M sodium hydroxide* is equivalent to 0.1907 g of $Na_2B_4O_7,10H_2O$.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Boric Acid

General Notices

(Ph. Eur. monograph 0001)

H_3BO_3 61.8 *10043-35-3*

Ph Eur

DEFINITION

Content

99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder, colourless, shiny plates greasy to the touch, or white or almost white crystals.

Solubility

Soluble in water and in ethanol (96 per cent), freely soluble in boiling water and in glycerol (85 per cent).

IDENTIFICATION

A. Dissolve 0.1 g by gently heating in 5 mL of *methanol R*, add 0.1 mL of *sulfuric acid R* and ignite the solution. The flame has a green border.

B. Solution S (see Tests) is acid (*2.2.4*).

TESTS

Solution S

Dissolve 3.3 g in 80 mL of boiling *distilled water R*, cool and dilute to 100 mL with *carbon dioxide-free water R* prepared from *distilled water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

www.webofpharma.com

https://thuocngocanh.com/

3.8 to 4.8 for solution S.

Solubility in ethanol (96 per cent)

The solution is not more opalescent than reference suspension II (2.2.1) and is colourless (2.2.2, Method II).

Dissolve 1.0 g in 10 mL of boiling *ethanol (96 per cent) R*.

Organic matter

It does not darken on progressive heating to dull redness.

Sulfates (2.4.13)

Maximum 450 ppm.

Dilute 10 mL of solution S to 15 mL with *distilled water R*.

ASSAY

Dissolve 1.000 g with heating in 100 mL of *water R* containing 15 g of *mannitol R*. Titrate with *1 M sodium hydroxide*, using 0.5 mL of *phenolphthalein solution R* as indicator, until a pink colour is obtained.

1 mL of *1 M sodium hydroxide* is equivalent to 61.8 mg of H_3BO_3.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Botulinum Toxin Type A for Injection

General Notices

(Ph. Eur. monograph 2113)

Ph Eur

DEFINITION

Botulinum toxin type A for injection is a dried preparation containing purified botulinum neurotoxin type A, which may be present in the form of a complex with haemagglutinins and non-toxic proteins. Botulinum neurotoxin type A or its haemagglutinin complex is prepared by purification of the liquid supernatant from a broth culture of a suitable strain of *Clostridium botulinum* type A, using a suitable process.

The purified complexes consist of several proteins and can be of various sizes. The largest complex (relative molecular mass of about 900 000) consists of a 150 000 relative molecular mass neurotoxin, a 130 000 relative molecular mass non-toxic protein and various haemagglutinins with relative molecular masses ranging from 14 000 to 43 000. The purified toxin moiety is composed solely of the same 150 000 relative molecular mass neurotoxin as is found in the 900 000 relative molecular mass neurotoxin complex, which is initially produced as a single chain and further cleaved (nicked) by endogenous proteases into a fully active, disulfide-linked, 54 000 relative molecular mass light chain and a 97 000 relative molecular mass heavy chain.

The preparation is reconstituted before use, as stated on the label.

PRODUCTION

GENERAL PROVISIONS

The toxin is produced using seed cultures managed in a defined seed-lot system in which the ability to produce toxin is conserved. The production method must be shown to yield, consistently, a product whose activity and profile are comparable to those of lots shown in clinical studies to be of adequate safety and efficacy.

The production method and stability of the finished product and relevant intermediates are evaluated using the tests described below. These include the specific toxin activity per milligram of protein of purified toxin in an appropriate functional model of toxin activity and may be supported by tests confirming the presence of botulinum toxin type A, and, if appropriate, associated non-toxic proteins.

BACTERIAL SEED LOTS

A highly toxigenic strain of *C. botulinum* of known toxin type A and confirmed absence of genes encoding other botulinum toxins (particularly botulinum toxin types B and F), with known origin and history, is grown using suitable media. The bacterial strain, used for the master seed lot, shall be identified by historical records that include information on its origin and the tests used to characterise the strain. These will include morphological, cultural, biochemical, genetic and serological properties of the strain. The master seed lot and the

https://thuocngocanh.com/

working seed lot, where applicable, must be demonstrated to have identical profiles. Only a seed lot that complies with the following requirements may be used.

Identification

Each seed lot is identified as containing pure cultures of *C. botulinum* type A bacteria with no extraneous bacterial or fungal contamination.

Microbial purity

Each seed lot complies with the requirements for absence of contaminating micro-organisms. The purity of bacterial cultures is verified by methods of suitable sensitivity. These may include inoculation into suitable media and examination of colony morphology.

Phenotypic parameters

Each seed lot must have a known fatty acid profile, sugar fermentation profile (glucose, lactose, mannose, etc.) and proteolytic activity and must demonstrate relevant lipase, lecithinase and gelatinase activity.

Genetic purity

Each seed lot must have information on the toxin gene sequence and comply with requirements for the absence of other genes encoding other toxin serotypes.

Production of active toxin

A bacterial strain producing a high yield of active toxin, as determined by an acute toxicity assay, is suitable. The seed lots must have demonstrated the ability to produce at least a minimum toxicity level appropriate for the manufacturing process and scale.

MANUFACTURER'S REFERENCE PREPARATIONS

During development, reference preparations are established for subsequent verification of batch consistency during production and for control of the bulk purified toxin and finished product. They are derived from representative batches of botulinum toxin type A that are characterised as described under Bulk purified toxin.

The reference preparations are suitably characterised for their intended purpose and are stored in aliquots of an appropriate size under conditions ensuring their suitability.

BULK PURIFIED TOXIN

C. botulinum type A strain is grown anaerobically, in suitable media, from which cultures are selected for step-up incubations under a suitably controlled anaerobic atmosphere through the seed culture and bulk fermentation stages to allow maximum production of toxin. The toxin is then purified by suitable methods to remove nucleic acids and components likely to cause adverse reactions.

Only a purified toxin that complies with the following requirements may be used in the preparation of the final bulk. For each test and for each product, limits of acceptance are established and each new purified toxin must comply with these limits.

Residual reagents

www.webofpharma.com

https://thuocngocanh.com/

Removal of residual reagents used in purification steps is confirmed by suitable limit tests or by validation of the process.

Nucleic acids

Removal of nucleic acids is confirmed by suitable limit tests or by validation of the process.

Immunological identity

The presence of specific type A toxin is confirmed by a suitable immunochemical method (*2.7.1*).

Specific activity

The specific activity is confirmed in a mouse model of toxicity or, in the interests of animal welfare, by an *in vitro* method (e.g. a cell-based assay) validated with respect to the LD_{50} assay. The specific activity is expressed in mouse LD_{50} units per milligram of protein. It must not be less than 1×10^8 mouse LD_{50} units per milligram of protein for the 150 000 relative molecular mass neurotoxin and not less than 1×10^7 mouse LD_{50} units per milligram of protein for the 900 000 relative molecular mass neurotoxin complex.

Protein

The total protein concentration is determined by a suitable method. An acceptable value is established for the product and each batch must be shown to comply with the limits.

Protein profile

Identity and protein composition are determined by polyacrylamide gel electrophoresis (*2.2.31*) under reducing or non-reducing conditions or by other suitable physicochemical methods such as size-exclusion chromatography (*2.2.30*), by comparison with suitable reference standards.

Total viable count

It complies with the limits approved for the particular product.

FINAL BULK

The final bulk is prepared by adding approved excipients to the bulk purified toxin. The solution is filtered through a bacteria-retentive filter. If human albumin is added, it complies with the monograph *Human albumin solution (0255)*.

FINAL LOT

The final bulk is distributed aseptically into sterile, tamper-evident containers. Uniformity of fill is verified during filling and the test for uniformity of content (*2.9.6*) is not required. The containers are closed so as to prevent contamination.

Only a final lot that is within the limits approved for the particular product and is satisfactory with respect to each of the requirements given below under Identification, Tests and Assay may be released for use.

pH (*2.2.3*)

https://thuvienthuocngocanh.com/

The pH of the reconstituted product is within ± 0.5 pH units of the limit approved for the particular product.

Water

Not more than the limit approved for the particular product.

IDENTIFICATION

The presence of botulinum toxin type A is confirmed by a suitable immunochemical method (*2.7.1*).

TESTS

Sterility (*2.6.1*)

It complies with the test for sterility.

Bacterial endotoxins (*2.6.14*)

Less than 10 IU per vial.

ASSAY

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests must be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. The LD_{50} assay is associated with severe suffering of animals and manufacturers are strongly encouraged to develop and validate assays that will reduce the number of animals used, or to refine or replace the test procedure with the goal of promoting animal welfare.

The potency of the reconstituted product is determined by an LD_{50} assay in mice or by a method validated with respect to the LD_{50} assay. The potency is expressed in terms of the LD_{50} for mice or relative to the reference preparation.

To determine the LD_{50}, graded doses of the product are injected via the intraperitoneal route into groups of mice and the LD_{50} is calculated from the mouse lethality in each group by the usual statistical methods (*5.3*). A suitable reference preparation is assayed in parallel; the potency of the toxin is expressed relative to the reference or the value found for the reference is within suitable limits defined in terms of the assigned potency.

After validation with respect to the LD_{50} assay (reference method) and in the interests of animal welfare, the product may be assayed by an alternative *in vitro* method (e.g. a cell-based assay) that covers the mechanism of botulinum toxin activity.

For alternative methods the potency is calculated with respect to a suitable reference preparation calibrated in mouse LD_{50} units.

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the estimated potency.

www.webofpharma.com

https://thuocngocanh.com/

The test may be repeated but when more than 1 test is performed, the results of all valid tests must be combined in the estimate of potency.

Application of alternative end-points in the LD_{50} assay Where a laboratory has established an LD_{50} assay, the lethal end-point is replaced by observation of clinical signs and application of an end-point earlier than death to reduce animal suffering. The following is given as an example.

The progress of botulinum intoxication in mice following intraperitoneal injection can be represented by 6 stages defined by typical clinical signs:

Stage 1: increased rate of breathing;

Stage 2: increased rate of breathing, slight hollowing of the flanks;

Stage 3: increased rate of breathing, noticeable hollowing of the flanks, slight orbital tightening of the eyes;

Stage 4: difficulty in breathing, noticeable hollowing of the flanks, pilo-erection, abnormal gait and partial loss of mobility, moderate orbital tightening of the eyes;

Stage 5: very laboured breathing, severe hollowing of the flanks, pilo-erection, mouse is immobile and unresponsive to external stimuli (moribund state), definite orbital tightening of the eyes;

Stage 6: death.

The end-point stage is defined as the earliest stage that yields assay results equivalent to those obtained when a lethal end-point is applied, as established during validation. Mice are observed at defined intervals post-administration. Mice reaching the pre-defined end-point stage are removed and euthanised at specified observation times. The sum of euthanised animals and animals found dead is used to determine the LD_{50}.

The application of alternative end-points must be verified by each laboratory by scoring a suitable number of assays using both the clinical signs and the lethal end-point.

LABELLING

The label states:

— the number of units of toxin per vial with a statement that units are product specific and not applicable to other preparations containing botulinum toxin type A;

— the name and the volume of the diluent to be added for reconstitution of the dried product.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Botulinum Toxin Type B for Injection

General Notices

(Ph. Eur. monograph 2581)

Ph Eur

DEFINITION

Botulinum toxin type B for injection is a liquid preparation containing purified botulinum neurotoxin type B, which may be present in the form of a complex with haemagglutinins and non-toxic proteins. Botulinum neurotoxin type B or its haemagglutinin complex is prepared by a suitable purification process of the liquid supernatant from a broth-culture of a suitable strain of *Clostridium botulinum* type B. Suitable stabilisers may be added.

The toxin is present in its native form as a complex of neurotoxin and non-toxin proteins and haemagglutinins with a total relative molecular mass of approximately 700 000. The neurotoxin is synthesised by the bacterium as a single-chain polypeptide of approximately 150 000 relative molecular mass that is activated during the fermentation process via a proteolytic cleavage (nicking) by endogenous proteases. The nicked protein is a fully active double-chain polypeptide consisting of a heavy chain (100 000 relative molecular mass) and a light chain (50 000 relative molecular mass), connected by a disulfide bond.

PRODUCTION

GENERAL PROVISIONS

Production of the toxin is based on seed cultures, managed in a defined seed-lot system in which the ability to produce toxin is conserved. The production method must be shown to yield consistently product of activity and profile comparable to that of lots shown in clinical studies to be of adequate safety and efficacy.

The production method and stability of the finished product and relevant intermediates are evaluated using the tests below. Such tests include the specific toxin activity per milligram of protein of purified toxin in an appropriate functional model of toxin activity and may be supported by tests confirming the presence of botulinum toxin type B, and, if appropriate, associated non-toxic proteins.

BACTERIAL SEED LOTS

A highly toxigenic strain of *C. botulinum* of known toxin type B and confirmed absence of genes encoding other botulinum toxins (particularly botulinum toxin types A and F), with known origin and history, is grown using suitable media. The bacterial strain, used for the master seed lot, shall be identified by historical records that include information on its origin and the tests used to characterise the strain. These will include morphological, cultural, biochemical, genetic and serological properties of the strain. The master seed lot and the working seed lot, where applicable, must be demonstrated to have identical profiles. Only a seed lot that complies with the following requirements may be used.

www.webofpharma.com

https://thuocngocanh.com/

Identification

Each seed lot is identified as containing pure cultures of *C. botulinum* type B bacteria with no extraneous bacterial or fungal contamination.

Microbial purity

Each seed lot complies with the requirements for absence of contaminating micro-organisms. The purity of bacterial cultures is verified by methods of suitable sensitivity. These may include inoculation into suitable media and examination of colony morphology.

Phenotypic parameters

Each seed lot must have a known fatty acid profile, sugar fermentation profile (glucose, lactose, mannose, etc.) and proteolytic activity and must demonstrate relevant lipase, lecithinase and gelatinase activity.

Genetic purity

Each seed lot must have information on the toxin gene genomic location and on the toxin gene sequence, and comply with requirements for the absence of other genes encoding other toxin serotypes.

Production of active toxin

A bacterial strain producing a high yield of active toxin, as determined by an acute toxicity assay, is suitable. Seed lots demonstrate a capability of producing at least a minimum toxicity level appropriate for the manufacturing process and scale.

MANUFACTURER'S REFERENCE PREPARATIONS

During development, reference preparations are established for subsequent verification of batch consistency during production and for control of the bulk purified toxin and finished product. They are derived from representative batches of botulinum toxin type B that are characterised as described under Bulk Purified Toxin.

The reference preparations are suitably characterised for their intended purpose and are stored in suitably sized aliquots under conditions ensuring their suitability.

BULK PURIFIED TOXIN

C. botulinum type B strain is grown anaerobically, in suitable media, from which cultures are selected for step-up incubations under a suitably controlled anaerobic atmosphere through the seed culture and bulk fermentation stages to allow maximum production of toxin. The toxin is purified by suitable methods to remove nucleic acids and components likely to cause adverse reactions.

Only a purified toxin that complies with the following requirements may be used in the preparation of the final bulk. For each test and for each product, limits of acceptance are established and each new purified toxin must comply with these limits.

Residual reagents

Removal of residual reagents used in purification steps is confirmed by suitable limit tests or by validation of the process.

Nucleic acids

www.webofpharma.com

https://thuocngocanh.com/

Removal of nucleic acids is confirmed by suitable limit tests or by validation of the process.

Immunological identity

The presence of specific type B toxin is confirmed by a suitable immunochemical method (*2.7.1*).

Specific activity

The specific activity is confirmed in a mouse model of toxicity or by *in vivo/ex vivo* methods validated with respect to the LD_{50} assay and expressed in mouse LD_{50} units per milligram of protein. Specific activity must not be less than 1×10^8 mouse LD_{50} units per milligram of protein.

Protein

The total protein concentration is determined by a suitable method. An acceptable value is established for the product and each batch must be shown to comply with the limits.

Protein profile

Identity and protein composition are determined by polyacrylamide gel electrophoresis (*2.2.31*) under reducing or non-reducing conditions or by other suitable physicochemical methods such as size-exclusion chromatography (*2.2.30*), comparing with suitable reference standards.

Total viable count

It complies with the limits approved for the particular product.

FINAL BULK

The final bulk is prepared by adding approved excipients to the bulk purified toxin. The solution is filtered through a bacteria-retentive filter. If human albumin is added, it complies with the monograph *Human albumin solution (0255)*.

FINAL LOT

The final bulk is distributed aseptically into sterile, tamper-evident containers. Uniformity of fill is verified during filling and the test for uniformity of content (*2.9.6*) is not required. The containers are closed so as to prevent contamination.

Only a final lot that is within the limits approved for the particular product and is satisfactory with respect to each of the requirements given below under Identification, Tests and Assay may be released for use.

pH (*2.2.3*)

The pH of the product is within ± 0.5 pH units of the limit approved for the particular product.

IDENTIFICATION

The presence of botulinum toxin type B is confirmed by a suitable immunochemical method (*2.7.1*).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Sterility (*2.6.1*)

It complies with the test for sterility.

Bacterial endotoxins (*2.6.14*)

Less than 10 IU per vial.

ASSAY

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests must be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. The LD_{50} assay is associated with severe suffering of animals and manufacturers are strongly encouraged to develop and validate assays that will reduce the number of animals used, or refine or replace the test procedure with the goal of promoting animal welfare.

The potency of the product is determined by an LD_{50} assay in mice or by a method validated with respect to the LD_{50} assay. The potency is expressed in terms of the LD_{50} for mice or relative to the reference preparation.

For determination of the LD_{50}, graded doses of the product are injected intraperitoneally into groups of mice and the LD_{50} is calculated by the usual statistical methods (*5.3*) from the mouse lethality in each group. A suitable reference preparation is assayed in parallel; the potency of the toxin is expressed relative to the reference or the value found for the reference is within suitable limits defined in terms of the assigned potency.

After validation with respect to the LD_{50} assay (reference method), the product may also be assayed by other methods that are preferable in terms of animal welfare, for example mouse bioassays using paralysis as the end-point, *ex vivo* assays using mouse phrenic nerve diaphragm, endopeptidase assays *in vitro* and cell-based assays.

For alternative replacement methods the potency is calculated with respect to a suitable reference preparation calibrated in mouse LD_{50} units.

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the estimated potency.

The test may be repeated but when more than 1 test is performed, the results of all valid tests must be combined in the estimate of potency.

LABELLING

The label states the number of units of toxin per vial with a statement that units are product specific and not applicable to other preparations containing botulinum toxin type B.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bovine Serum

General Notices

(Ph. Eur. monograph 2262)

Ph Eur

DEFINITION

Liquid fraction of blood obtained from the ox (*Bos taurus* L.) and from which cells, fibrin and clotting factors have been removed.

Different types of bovine serum are used:

— *adult bovine serum* obtained at slaughter from cattle that are declared fit for human consumption;

— *calf serum* obtained at slaughter from animals, fit for human consumption, before the age of 12 months;

— *new-born calf serum* obtained at slaughter from animals before the age of 20 days;

— *foetal bovine serum* obtained from normal foetuses from dams fit for human consumption;

— *donor bovine serum* obtained by repeated bleeding of donor animals from controlled donor herds.

This monograph provides a general quality specification for bovine serum. Various measures are applied during the production of bovine serum aimed at obtaining a product that is acceptable as regards viral safety. No single measure, nor the combination of measures outlined below can guarantee complete viral safety but they rather reduce the risk involved in the use of serum in the manufacture of medicinal products. It is therefore necessary for the manufacturer of a medicinal product to take account of this when choosing the serum for a particular use by making a risk assessment.

PRODUCTION

All stages of serum production are submitted to a suitable quality management system.

Traceability of serum is maintained from the final container to the abattoir of origin (for blood collected from slaughtered animals) or to the herd of origin (for blood collected from donor animals).

Further guarantee of the safety and quality of serum may be ensured by the use of a controlled donor herd. Where serum is obtained from such a herd, the animals are subjected to regular veterinary examination to ascertain their health status. Animals introduced into the herd are traceable as regards source, breeding and rearing history. The introduction of animals into the herd follows specified procedures, including defined quarantine measures. During the quarantine period the animals are observed and tested to establish that they are free from all agents and antibodies from which the donor herd is claimed to be free. It may be necessary to test the animals in quarantine for freedom from additional agents, depending on factors such as information available on their breeding and rearing history. It is

www.webofpharma.com

https://thuocngocanh.com/

recommended that animals in the herd should not be vaccinated against bovine viral diarrhoea virus. Tests are carried out for any agent and/or antibody from which the herd is claimed to be free.

Serum is obtained by separation of the serum from blood cells and clot under conditions designed to minimise microbial contamination. Serum from a number of animals is pooled and a batch number is allocated to the pool. Appropriate steps are taken to ensure homogeneity of the harvested material, intermediate pools and the final batch. Suitable measures (for example filtration) are taken to ensure sterility or a low bioburden. Before further processing, the serum is tested for sterility or bioburden. General and specific tests for viral contaminants are carried out as described below.

A step or steps for virus inactivation/removal are applied to serum intended for production of immunological veterinary medicinal products. Unless otherwise justified and authorised for a particular medicinal product, a step or steps for virus inactivation/removal are applied to serum intended for production of human and non-immunological veterinary medicinal products.

INACTIVATION

The inactivation procedure applied is validated with respect to a suitable representative range of viruses covering different types (enveloped, non-enveloped, DNA, RNA viruses). The optimal choice of relevant and model viruses depends strongly on the specific inactivation/removal procedure; representative viruses with different degrees of resistance to the type of treatment must be included. Bovine viral diarrhoea virus must be included in the viruses used for validation. Serum free from antibodies against bovine viral diarrhoea virus is used in part or all of the validation studies.

For bovine serum intended for use in immunological veterinary medicinal products, for inactivation by gamma irradiation a minimum dose of 30 kGy is applied, unless otherwise justified and authorised.

Critical parameters for the method of virus inactivation/removal are established and the parameters used in the validation study are strictly adhered to during subsequent application of the procedures to each batch of serum.

For inactivation by gamma irradiation, critical parameters include:

— the temperature;

— packaging configuration;

— distribution of dosimeters to assess the effective dose received by the product whatever its position;

— the minimum and maximum dose received.

QUALITY CONTROL TESTS APPLIED TO EACH BATCH

A suitable sample size for each batch is established. Specific tests for viral contaminants are validated with respect to sensitivity and specificity. The cell cultures used for general tests for viral contaminants are shown to be sensitive to a suitable range of potential contaminants. Control cells used in the tests are cultivated, where relevant, with a bovine serum controlled and inactivated as described in this monograph. Serum free from antibodies to bovine viral diarrhoea virus is required for validation of the effect of antibodies on the detection limits for bovine viral diarrhoea virus.

www.webofpharma.com

https://thuocngocanh.com/

Tests carried out on the batch prior to treatment

The following tests are carried out on the serum (before any virus inactivation/removal steps, where applicable).

Tests for viral contaminants General tests supplemented by specific tests are carried out.

General tests Validated tests are carried out by inoculation of the serum on at least 2 distinct cell lines, one of which is of bovine origin. The cell lines used are suitable for detecting haemadsorbing viruses such as bovine parainfluenza virus 3 and cytopathic agents such as bovine herpesvirus 1.

Specific tests for viral contaminants (if not detected by general tests), where relevant in view of the country of origin of the serum Bluetongue virus, bovine adenovirus, bovine parvovirus, bovine respiratory syncytial virus, bovine viral diarrhoea virus, rabies virus and reovirus. Depending on the country of origin, specific tests for other viruses may be needed. The animal health status of countries is defined by the 'Office International des Epizooties' (OIE).

For serum to be subjected to a virus inactivation/removal procedure, if evidence of viral contamination is found in any of the tests described above, the serum is acceptable only if the virus is identified and shown to be present in an amount that has been shown in a validation study to be effectively inactivated.

For serum that is not to be subjected to a virus inactivation/removal procedure, if evidence of viral contamination is found in any of the tests described above, the serum is not acceptable.

A test for bovine viral diarrhoea virus antibodies is carried out; an acceptance criterion for the titre is established taking account of the risk assessment.

Composition The content of a suitable selection of the following components is determined and shown to be within the expected range for the type of serum: cholesterol, α-, β- and γ-globulin, albumin, creatinine, bilirubin, glucose, serum aspartate transaminase (SAST, formerly SGOT - serum glutamic-oxaloacetic transaminase), serum alanine transaminase (SALT, formerly SGPT - glutamic-pyruvic transaminase), phosphorus, potassium, calcium, sodium and pH.

Tests carried out on the batch post-treatment

If bovine viral diarrhoea virus was detected before virus inactivation/removal, the following test for bovine viral diarrhoea virus is carried out after virus inactivation/removal.

Test for bovine viral diarrhoea virus A validated test for bovine viral diarrhoea virus is carried out, for example by inoculation into susceptible cell cultures, followed by not fewer than 3 subcultures and detection by immunostaining. No evidence of the presence of bovine viral diarrhoea virus is found.

IDENTIFICATION

A. The electrophoretic pattern corresponds to that for serum and is consistent with the type (foetal or other) of bovine serum.

B. Bovine origin is confirmed by a suitable immunochemical method (*2.7.1*).

TESTS

Osmolality (*2.2.35*)

www.webofpharma.com

https://thuvienthuocngocanh.com/

280 mosmol/kg to 365 mosmol/kg for foetal bovine serum and 240 mosmol/kg to 340 mosmol/kg for other types.

Total protein (*2.5.33*)

30 mg/mL to 45 mg/mL for foetal bovine serum and minimum 35 mg/mL for other types.

Haemoglobin

Maximum 4 mg/mL, determined by a validated method, such as spectrophotometry.

Bacterial endotoxins (*2.6.14*)

Less than 10 IU/mL for donor bovine serum, less than 25 IU/mL for foetal bovine serum, less than 100 IU/mL for other types.

Sterility (*2.6.1*)

It complies with the test. Use 10 mL for each medium.

Mycoplasmas (*2.6.7*)

It complies with the test.

STORAGE

Frozen at -10 °C or below.

LABELLING

The label states:

— the type of serum;

— where applicable, that the serum has been inactivated and the inactivation method;

— where the serum has been inactivated by gamma irradiation, the target minimum dose of the irradiation procedure.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

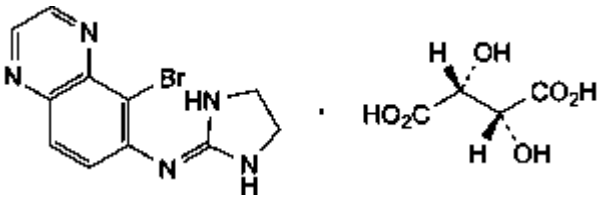
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Brimonidine Tartrate

General Notices

(Ph. Eur. monograph 2760)



$C_{15}H_{16}BrN_5O_6$ 442.2 *70359-46-5*

Action and use

Alpha$_2$-adrenoceptor agonist; treatment of hypertension.

Ph Eur

DEFINITION

5-Bromo-*N*-(imidazolidin-2-ylidene)quinoxalin-6-amine (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish or slightly brownish powder.

Solubility

Soluble in water, practically insoluble in anhydrous ethanol and in toluene.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *brimonidine tartrate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Specific optical rotation (2.2.7)

+ 9.0 to + 10.5 (dried substance).

Dissolve 0.50 g in *water R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 65.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve the contents of a vial of *brimonidine for system suitability CRS* (containing impurity E) in 1.0 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Dissolve 2.6 g of *sodium heptanesulfonate R* in 310 mL of *methanol R*, add 2.5 mL of *triethylamine R* and 7.5 mL of *glacial acetic acid R*, and dilute to 1000 mL with *water R*. Use a freshly prepared mixture.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 264 nm.

Injection 20 µL.

Run time 3 times the retention time of brimonidine.

Identification of impurities Use the chromatogram supplied with *brimonidine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention With reference to brimonidine (retention time = about 19 min): impurity E = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity E and brimonidine.

Calculation of percentage contents:

https://thuocngocanh.com/

— for each impurity, use the concentration of brimonidine tartrate in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

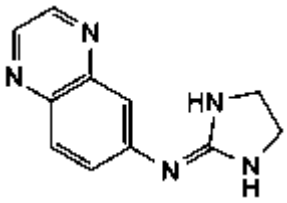
ASSAY

Dissolve 0.350 g in 70 mL of *anhydrous acetic acid R* using sonication until complete dissolution. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 44.22 mg of $C_{15}H_{16}BrN_5O_6$.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G.*

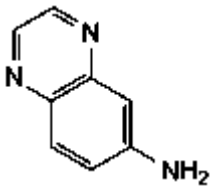


A. *N*-(imidazolidin-2-ylidene)quinoxalin-6-amine,

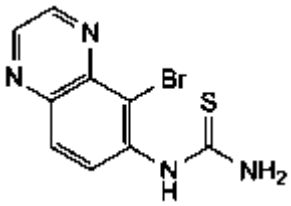
B. 5-bromoquinoxalin-6-amine,

www.webofpharma.com

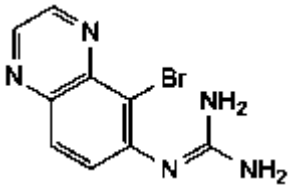
https://thuocngocanh.com/



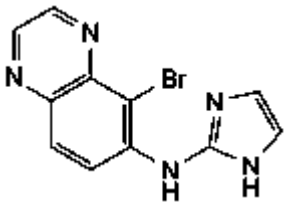
C. quinoxalin-6-amine,



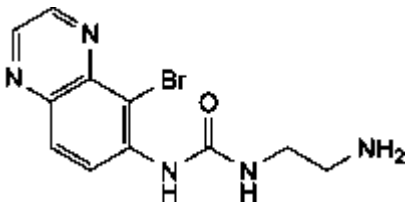
D. 1-(5-bromoquinoxalin-6-yl)thiourea,



E. 2-(5-bromoquinoxalin-6-yl)guanidine,



F. 5-bromo-*N*-(1*H*-imidazol-2-yl)quinoxalin-6-amine,



G. 1-(2-aminoethyl)-3-(5-bromoquinoxalin-6-yl)urea.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bromazepam

General Notices

(Ph. Eur. monograph 0879)

$C_{14}H_{10}BrN_3O$ 316.2 *1812-30-2*

Action and use

Benzodiazepine.

Ph Eur

DEFINITION

7-Bromo-5-(pyridin-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble or sparingly soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *bromazepam CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture Mix 1 volume of *acetonitrile R* and 8 volumes of *methanol R*.

Test solution Dissolve 10.0 mg of the substance to be examined in 9 mL of the solvent mixture. Dilute to 20.0 mL with an 11.33 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 7.0 with a 100 g/L solution of *potassium hydroxide R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *bromazepam for system suitability A CRS* (containing impurities A and C) in 5 mL of the solvent mixture. Dilute to 10 mL with an 11.33 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 7.0 with a 100 g/L solution of *potassium hydroxide R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 50 °C.

Mobile phase Mix 5 volumes of *acetonitrile for chromatography R*, 45 volumes of *methanol R1* and 50 volumes of an 11.33 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 7.0 with a 100 g/L solution of *potassium hydroxide R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Run time 4 times the retention time of bromazepam.

Identification of impurities Use the chromatogram supplied with *bromazepam for system suitability A CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention With reference to bromazepam (retention time = about 5 min): impurity A = about 1.5; impurity C = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 1.2 between the peaks due to impurities A and C.

Calculation of percentage contents:

www.webofpharma.com

https://thuvienthuocngocanh.com/

— for each impurity, use the concentration of bromazepam in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 20 mL of *anhydrous acetic acid R*. Add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

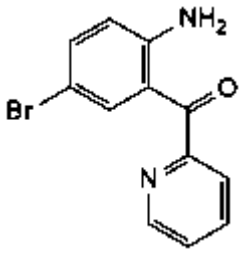
1 mL of *0.1 M perchloric acid* is equivalent to 31.62 mg of $C_{14}H_{10}BrN_3O$.

STORAGE

Protected from light.

IMPURITIES

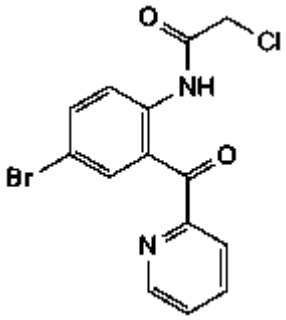
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E.



A. (2-amino-5-bromophenyl)(pyridin-2-yl)methanone,

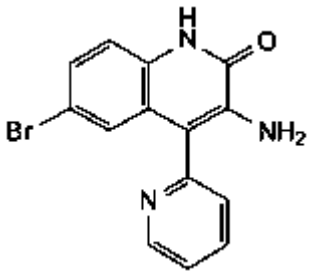
www.webofpharma.com

https://thuocngocanh.com/

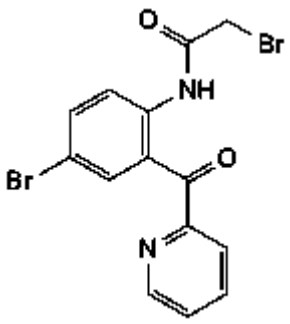


B. *N*-[4-bromo-2-(pyridine-2-carbonyl)phenyl]-2-chloroacetamide,

C. 7-bromo-5-(6-methylpyridin-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,



D. 3-amino-6-bromo-4-(pyridin-2-yl)quinolin-2(1*H*)-one,



E. 2-bromo-*N*-[4-bromo-2-(pyridine-2-carbonyl)phenyl]acetamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

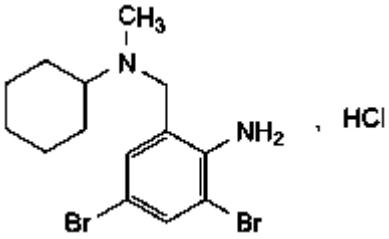
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bromhexine Hydrochloride

General Notices

(Ph. Eur. monograph 0706)



$C_{14}H_{21}Br_2ClN_2$ 412.6 *611-75-6*

Action and use

Mucolytic.

Ph Eur

DEFINITION

2,4-Dibromo-6-[[cyclohexyl(methyl)amino]methyl]aniline hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, C.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *bromhexine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 10 mg of *bromhexine hydrochloride CRS* in *methanol R* and dilute to 5.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *2-propanol R*, *acetone R* (1:29:70 *V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve about 20 mg in 1 mL of *methanol R* and add 1 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 0.6 g in *methanol R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 1.26 g of *ammonium formate R* in 950 mL of *water for chromatography R* and adjust to pH 4.4 with *anhydrous formic acid R*. Dilute to 1000.0 mL with *water for chromatography R*.

Solvent mixture *acetonitrile for chromatography R*, *water for chromatography R* (50:50 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *bromhexine for system suitability CRS* (containing impurities C and D) in the solvent mixture and dilute to 2.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of *bromhexine hydrochloride CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped solid core octadecylsilyl silica gel for chromatography R* (2.6 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile for chromatography R*, buffer solution (40:60 *V/V*).

Flow rate 0.2 mL/min.

Detection Spectrophotometer at 248 nm.

Injection 3.0 µL of test solution (a) and reference solutions (a) and (b).

Run time Twice the retention time of bromhexine.

Identification of impurities Use the chromatogram supplied with *bromhexine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and D.

Relative retention With reference to bromhexine (retention time = about 10 min): impurity C = about 0.2; impurity D = about 0.3.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities C and D.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity C by 1.6;

— for each impurity, use the concentration of bromhexine hydrochloride in reference solution (b).

Limits:

— *impurity C*: maximum 0.15 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{14}H_{21}Br_2ClN_2$ taking into account the assigned content of *bromhexine hydrochloride CRS*.

STORAGE

Protected from light.

IMPURITIES

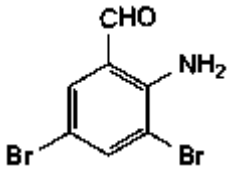
Specified impurities *C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, D, E.*

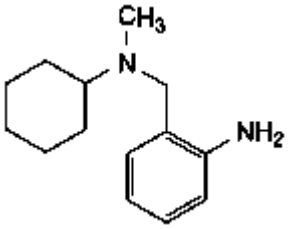
A. (2-amino-3,5-dibromophenyl)methanol,

www.webofpharma.com

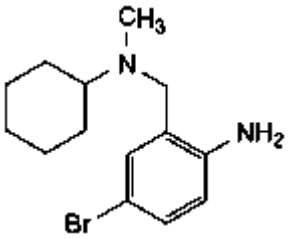
https://thuocngocanh.com/



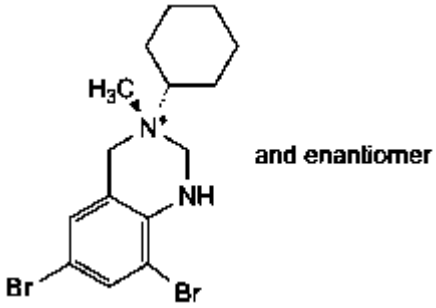
B. 2-amino-3,5-dibromobenzaldehyde,



C. 2-[[cyclohexyl(methyl)amino]methyl]aniline,



D. 4-bromo-2-[[cyclohexyl(methyl)amino]methyl]aniline,



E. (3*RS*)-6,8-dibromo-3-cyclohexyl-3-methyl-1,2,3,4-tetrahydroquinazolin-3-ium.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bromocriptine Capsules

General Notices

Action and use

Dopamine receptor agonist.

DEFINITION

Bromocriptine Capsules contain Bromocriptine Mesilate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

Content of bromocriptine, $C_{32}H_{40}BrN_5O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing the equivalent of 10 mg of bromocriptine with 50 mL of *methanol* for 30 minutes, centrifuge and dilute 5 mL of the supernatant liquid to 20 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 380 nm exhibits a maximum at 305 nm and a minimum at 270 nm.

B. In the test for Related substances, the principal band in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (6).

C. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions, prepare the solutions in subdued light and immediately before use. Apply solution (1) as the last solution and develop the chromatograms immediately in an unsaturated tank.

(1) Shake a quantity of the contents of the capsules containing the equivalent of 20 mg of bromocriptine with 10 mL of *methanol* for 20 minutes and centrifuge.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of solution (1) to 10 volumes with *methanol*.

(3) Dilute 3 volumes of solution (1) to 100 volumes with *methanol*.

(4) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(5) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

(6) 0.023% w/v of *bromocriptine mesilate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution as 10-mm bands.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of cold air for 2 minutes, spray with *ammonium molybdate solution R3* and heat at 100° until bands appear (about 10 minutes).

MOBILE PHASE

0.1 volumes of 13.5M *ammonia*, 1.5 volumes of *water*, 3 volumes of *propan-2-ol*, 88 volumes of *dichloromethane* and 100 volumes of *ether*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary band* is not more intense than the band in the chromatogram obtained with solution (3) (3%);

not more than one such band is more intense than the band in the chromatogram obtained with solution (4) (1%);

not more than a further two such bands are more intense than the band in the chromatogram obtained with solution (5) (0.5%).

Disregard any band within 20 mm of the line of application.

ASSAY

Prepare the solutions in subdued light. Weigh and powder the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the capsule contents containing the equivalent of 10 mg of bromocriptine with 70 mL of *methanol (50%)* with the aid of ultrasound for 5 minutes, filter and dilute to 100 mL with the same solvent.

(2) 0.011% w/v of *bromocriptine mesilate BPCRS* in *methanol (50%)*.

(3) Heat a 0.011% w/v solution of *bromocriptine mesilate BPCRS* in a mixture of 1 volume of 1M *acetic acid* and 9 volumes of *methanol* at 60° for 90 minutes and cool to room temperature.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use ambient column temperature.

(e) Use a detection wavelength of 300 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of a 0.08% w/v solution of *ammonium carbonate* and 55 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The assay is not valid unless the *resolution factor* between the two peaks obtained with solution (3) is not less than 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{32}H_{40}BrN_5O_5$ using the declared content of $C_{32}H_{40}BrN_5O_5$ in *bromocriptine mesilate BPCRS*.

STORAGE

Bromocriptine Capsules should be kept in an airtight container and protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of bromocriptine.

© Crown Copyright 2022

www.webofpharma.com

https://thuvienthuocngocanh.com/

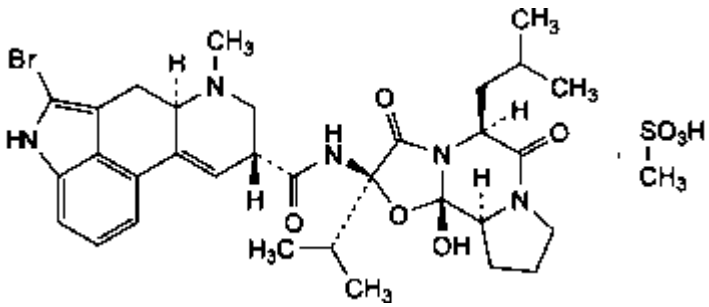
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Bromocriptine Mesilate

General Notices

(Ph. Eur. monograph 0596)



$C_{33}H_{44}BrN_5O_8S$ 751 *22260-51-1*

Action and use

Dopamine receptor agonist.

Preparations

Bromocriptine Capsules

Bromocriptine Tablets

Ph Eur

DEFINITION

(5′*S*,8*R*)-2-Bromo-12′-hydroxy-5′-(2-methylpropyl)-2′-(propan-2-yl)ergotaman-3′,6′,18-trione methanesulfonate.

Content

98.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in bromocriptine mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in*

www.webofpharma.com

https://thuocngocanh.com/

methanesulfonic acid, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

White or slightly coloured, fine crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), sparingly soluble in methylene chloride.

It is very sensitive to light.

The identification, tests and assay are to be carried out as rapidly as possible, protected from light.

IDENTIFICATION

First identification: B.

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution Dissolve 10.0 mg in 10 mL of *methanol R* and dilute to 200.0 mL with *0.01 M hydrochloric acid*.

Spectral range 250-380 nm.

Absorption maximum At 305 nm.

Absorption minimum At 270 nm.

Specific absorbance at the absorption maximum 120 to 135 (dried substance).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *bromocriptine mesilate CRS*.

C. Thin-layer chromatography (*2.2.27*). *Prepare the solutions immediately before use*.

Solvent mixture *ethanol (96 per cent) R*, *methanol R*, *methylene chloride R* (30:30:40 *V/V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution Dissolve 10 mg of *bromocriptine mesilate CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *water R*, *2-propanol R*, *methylene chloride R*, *ether R* (0.1:1.5:3:88:100 *V/V/V/V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Application 10 µL.

Development Immediately in an unsaturated tank, over a path of 15 cm.

Drying In a current of cold air for 2 min.

Detection Spray with *ammonium molybdate solution R3* and dry at 100 °C until the spots appear (about 10 min).

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. To 0.1 g add 5 mL of *dilute hydrochloric acid R* and shake for about 5 min. Filter and add 1 mL of *barium chloride solution R1*. The filtrate remains clear. To a further 0.1 g add 0.5 g of *anhydrous sodium carbonate R*, mix and ignite until a white residue is obtained. Allow to cool and dissolve the residue in 7 mL of *water R* (solution A). Solution A gives reaction (a) of sulfates (*2.3.1*).

E. Solution A obtained in identification test D gives reaction (a) of bromides (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_5, BY_5 or Y_5 (*2.2.2, Method II*).

Dissolve 0.25 g in *methanol R* and dilute to 25 mL with the same solvent.

pH (*2.2.3*)

3.1 to 3.8.

Dissolve 0.2 g in a mixture of 2 volumes of *methanol R* and 8 volumes of *carbon dioxide-free water R* and dilute to 20 mL with the same mixture of solvents.

Specific optical rotation (*2.2.7*)

+ 95 to + 105 (dried substance).

Dissolve 0.100 g in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 10.0 mL with the same mixture of solvents.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *buffer solution pH 2.0 R*, *methanol R* (50:50 *V/V*).

Test solution Dissolve 0.500 g of the substance to be examined in 5.0 mL of *methanol R* and dilute to 10.0 mL with *buffer solution pH 2.0 R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *bromocriptine mesilate for system suitability CRS* (containing impurities A and B) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.12 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 0.791 g/L solution of *ammonium carbonate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	90 → 40	10 → 60
30 - 45	40	60

Flow rate 2 mL/min.

Detection Spectrophotometer at 300 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *bromocriptine mesilate for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to bromocriptine: impurity C = about 1.2.

System suitability Reference solution (c):

— *resolution*: minimum 1.1 between the peaks due to impurities A and B.

Limits:

— *impurity A*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent);

— *impurity C*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurities B, D, E, F, G*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and not more than 1 such peak has an area greater than the area of the principal peak in the

www.webofpharma.com

https://thuvienthuocngocanh.com/

chromatogram obtained with reference solution (b) (0.1 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent), apart from the peak due to impurity A.

Loss on drying (2.2.32)

Maximum 3.0 per cent, determined on 0.500 g by drying *in vacuo* at 80 °C for 5 h.

ASSAY

Dissolve 0.500 g in 80 mL of a mixture of 10 volumes of *anhydrous acetic acid R* and 70 volumes of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

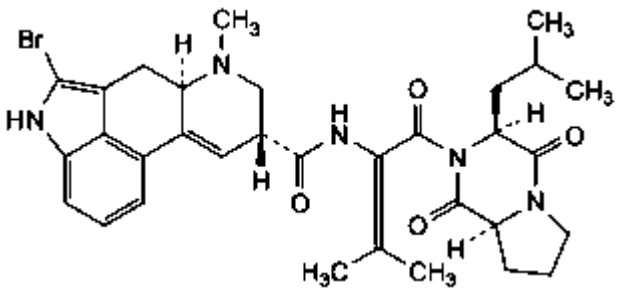
1 mL of *0.1 M perchloric acid* is equivalent to 75.1 mg of $C_{33}H_{44}BrN_5O_8S$.

STORAGE

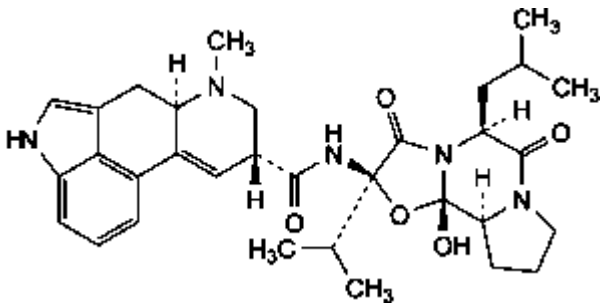
In an airtight container, protected from light, at a temperature not exceeding -15 °C.

IMPURITIES

Specified impurities A, B, C, D, E, F, G.



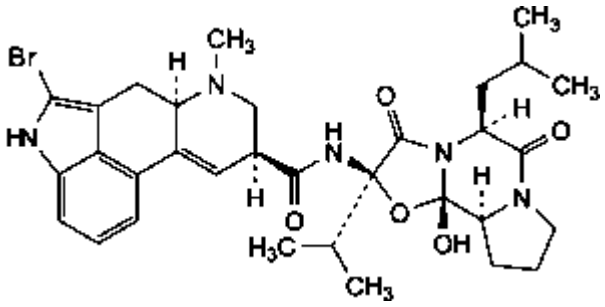
A. (8*R*)-2-bromo-6-methyl-*N*-[3-methyl-1-[(3*S*,8a*S*)-3-(2-methylpropyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-1-oxobut-2-en-2-yl]-9,10-didehydroergoline-8-carboxamide,



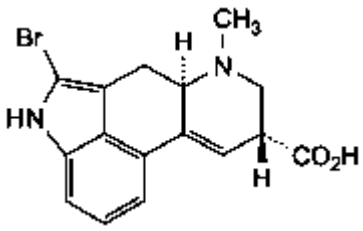
B. (5′*S*,8*R*)-12′-hydroxy-5′-(2-methylpropyl)-2′-(propan-2-yl)ergotaman-3′,6′,18-trione,

www.webofpharma.com

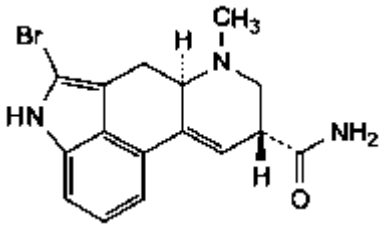
https://thuocngocanh.com/



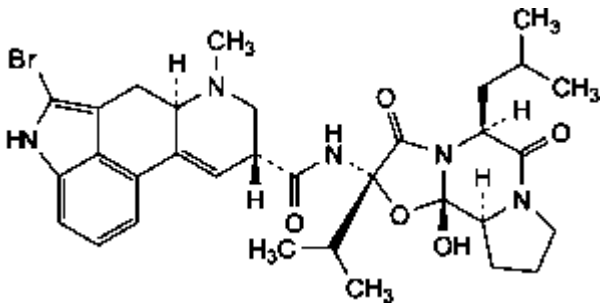
C. (5′*S*,8*S*)-2-bromo-12′-hydroxy-5′-(2-methylpropyl)-2′-(propan-2-yl)ergotaman-3′,6′,18-trione,



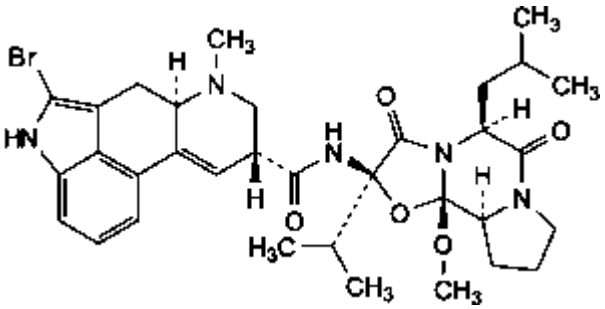
D. (8*R*)-2-bromo-6-methyl-9,10-didehydroergoline-8-carboxylic acid,



E. (8*R*)-2-bromo-6-methyl-9,10-didehydroergoline-8-carboxamide,



F. (2′*S*,5′*S*,8*R*)-2-bromo-12′-hydroxy-5′-(2-methylpropyl)-2′-(propan-2-yl)ergotaman-3′,6′,18-trione,



G. (5′*S*,8*R*)-2-bromo-12′-methoxy-5′-(2-methylpropyl)-2′-(propan-2-yl)ergotaman-3′,6′,18-trione.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bromocriptine Tablets

General Notices

Action and use

Dopamine receptor agonist.

DEFINITION

Bromocriptine Tablets contain Bromocriptine Mesilate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

Content of bromocriptine, $C_{32}H_{40}BrN_5O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 10 mg of bromocriptine with 50 mL of *methanol* for 30 minutes, centrifuge and dilute 5 mL of the supernatant liquid to 20 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 380 nm exhibits a maximum at 305 nm and a minimum at 270 nm.

B. In the test for Related substances, the principal band in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (6).

C. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 10 mg of bromocriptine with 25 mL of a mixture of equal volumes of *chloroform* and *methanol* for 30 minutes, filter through a sintered-glass filter (ISO 4793, porosity grade 4, is suitable) and wash

www.webofpharma.com

https://nhathuocngocanh.com/

the residue with two 5-mL quantities of the solvent mixture. Evaporate the filtrate and washings to dryness at 25° at a pressure of 2 kPa, dissolve the residue in 2 mL of the solvent mixture and centrifuge.

(2) Dilute 1 volume of solution (1) to 10 volumes with a mixture of equal volumes of *chloroform* and *methanol*.

(3) Dilute 3 volumes of solution (2) to 10 volumes with a mixture of equal volumes of *chloroform* and *methanol*.

(4) Dilute 1 volume of solution (2) to 10 volumes with a mixture of equal volumes of *chloroform* and *methanol*.

(5) Dilute 1 volume of solution (2) to 20 volumes with a mixture of equal volumes of *chloroform* and *methanol*.

(6) 0.055% w/v of *bromocriptine mesilate BPCRS* in a mixture of equal volumes of *chloroform* and *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution as 10-mm bands.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air for 2 minutes, spray with *ammonium molybdate solution R3* and heat at 100° until bands appear (about 10 minutes).

MOBILE PHASE

0.1 volumes of 13.5M *ammonia*, 1.5 volumes of *water*, 3 volumes of *propan-2-ol*, 88 volumes of *dichloromethane* and 100 volumes of *ether*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary band* is not more intense than the band in the chromatogram obtained with solution (3) (3%);

not more than one such band is more intense than the band in the chromatogram obtained with solution (4) (1%);

not more than a further two such bands are more intense than the band in the chromatogram obtained with solution (5) (0.5%).

Disregard any band within 20 mm of the line of application.

Uniformity of content

Tablets containing less than the equivalent of 2 mg and/or less than 2% w/w of bromocriptine comply with the requirements stated under Tablets using the following method of analysis. Mix one tablet with 50 mL of *ethanol (50%)* with the aid of ultrasound until disintegrated, shake for 30 minutes and centrifuge. Measure the *absorbance* of the supernatant liquid at the maximum at 305 nm, Appendix II B. Calculate the content of $C_{32}H_{40}BrN_5O_5$ taking 144 as the value of A(1%, 1 cm) at the maximum at 305 nm.

ASSAY

Prepare the solutions in subdued light. Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing the equivalent of 10 mg of bromocriptine with 70 mL of *methanol (50%)* with the aid of ultrasound for 5 minutes, shake for 30 minutes, filter and dilute to 100 mL with the same solvent.

(2) 0.011% w/v of *bromocriptine mesilate BPCRS* in *methanol (50%)*.

www.webofpharma.com

https://thuocngocanh.com/

(3) Heat a 0.011% w/v solution of *bromocriptine mesilate BPCRS* in a mixture of 1 volume of 1M *acetic acid* and 9 volumes of *methanol* at 60° for 90 minutes and cool to room temperature.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 300 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

45 volumes of a 0.08% w/v solution of *ammonium carbonate* and 55 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The assay is not valid unless the *resolution factor* between the two peaks obtained with solution (3) is not less than 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{32}H_{40}BrN_5O_5$ in the tablets using the declared content of $C_{32}H_{40}BrN_5O_5$ in *bromocriptine mesilate BPCRS*.

STORAGE

Bromocriptine Tablets should be kept in an airtight container and protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of bromocriptine.

© Crown Copyright 2022

www.webofpharma.com

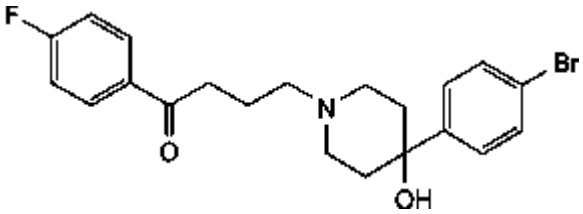
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bromperidol

General Notices

(Ph. Eur. monograph 1178)



$C_{21}H_{23}BrFNO_2$ 420.3 *10457-90-6*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

4-[4-(4-Bromophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, sparingly soluble in methanol and in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

https://thuocngocanh.com/

A. Melting point (2.2.14): 156 °C to 159 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison bromperidol CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of bromperidol CRS in methanol R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of bromperidol CRS and 10 mg of haloperidol CRS in methanol R and dilute to 10 mL with the same solvent.

Plate TLC octadecylsilyl silica gel plate R.

Mobile phase tetrahydrofuran R, methanol R, 58 g/L solution of sodium chloride R (10:45:45 *V/V/V*).

Application 1 µL.

Development In an unsaturated tank, over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 spots which may, however, not be completely separated.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 10 mg in 5 mL of anhydrous ethanol R. Add 0.5 mL of dinitrobenzene solution R and 0.5 mL of 2 M alcoholic potassium hydroxide R. A violet colour is produced that becomes brownish-red after 20 min.

E. To 0.1 g in a porcelain crucible add 0.5 g of anhydrous sodium carbonate R. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of dilute nitric acid R and filter. To 1 mL of the filtrate add 1 mL of water R. The solution gives reaction (a) of bromides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, Method II).

Dissolve 0.2 g in 20 mL of a 1 per cent *V/V* solution of lactic acid R.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in methanol R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2.5 mg of bromperidol CRS and 5.0 mg of haloperidol CRS in methanol R and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with methanol R. Dilute 1.0 mL of this solution to 10.0 mL with methanol R.

Column:

— *size*: *l* = 0.1 m, Ø = 4.0 mm;

— *stationary phase*: base-deactivated octadecylsilyl silica gel for chromatography R (3 µm).

Mobile phase:

— *mobile phase A*: 17 g/L solution of tetrabutylammonium hydrogen sulfate R;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	90 → 50	10 → 50
15 - 20	50	50
20 - 25	90	10

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Relative retention With reference to bromperidol (retention time = about 6 min): impurity A = about 0.5; impurity B = about 0.8; haloperidol = about 0.9; impurity C = about 1.4; impurity D = about 1.5; impurity E = about 1.8; impurity F = about 1.85.

System suitability Reference solution (a):

— resolution: minimum 3.0 between the peaks due to haloperidol and bromperidol.

Limits:

— *impurities A, B, C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

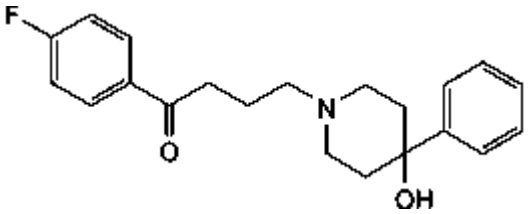
1 mL of *0.1 M perchloric acid* is equivalent to 42.03 mg of $C_{21}H_{23}BrFNO_2$.

STORAGE

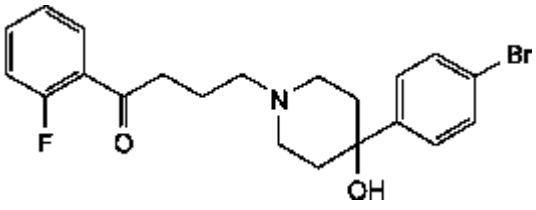
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*



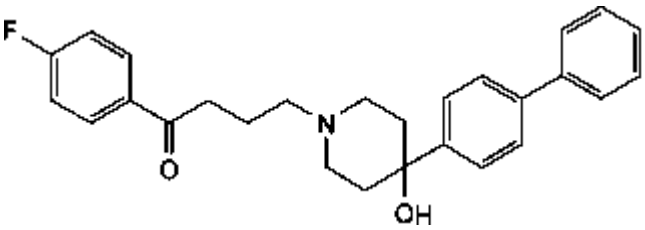
A. 1-(4-fluorophenyl)-4-(4-hydroxy-4-phenylpiperidin-1-yl)butan-1-one,



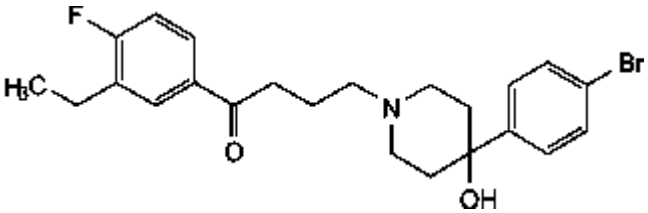
B. 4-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]-1-(2-fluorophenyl)butan-1-one,

www.webofpharma.com

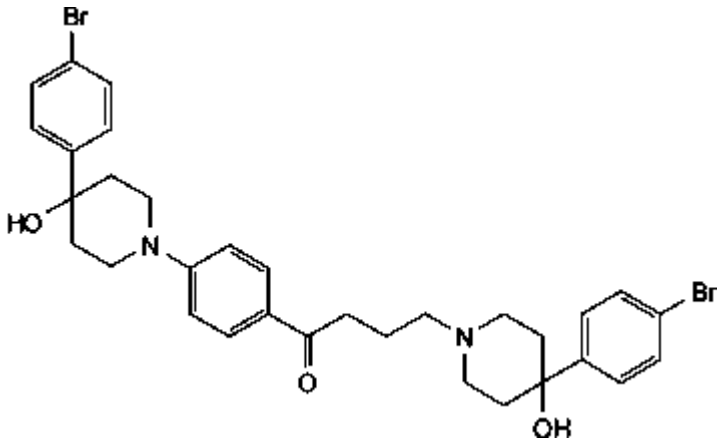
https://thuocngocanh.com/



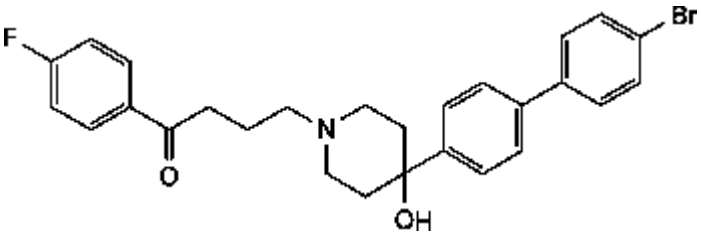
C. 4-[4-(biphenyl-4-yl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one,



D. 4-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]-1-(3-ethyl-4-fluorophenyl)butan-1-one,



E. 4-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]-1-[4-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]phenyl]butan-1-one,



F. 4-[4-(4′-bromobiphenyl-4-yl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

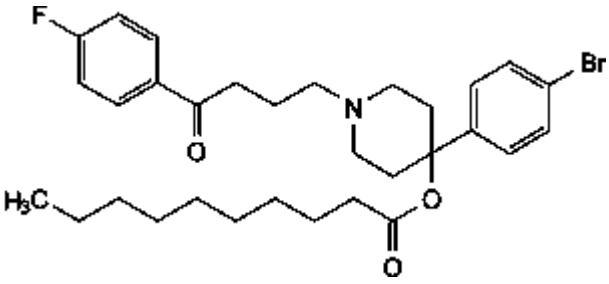
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bromperidol Decanoate

General Notices

(Ph. Eur. monograph 1397)



$C_{31}H_{41}BrFNO_3$ 574.6 *75067-66-2*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

4-(4-Bromophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl decanoate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, very soluble in methylene chloride, soluble in ethanol (96 per cent).

mp

About 60 °C.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *bromperidol decanoate CRS*.

B. To 0.1 g in a porcelain crucible add 0.5 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 5 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of bromides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_5 (2.2.2, *Method II*).

Dissolve 2.0 g in *methylene chloride R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2.5 mg of *bromperidol decanoate CRS* and 2.5 mg of *haloperidol decanoate CRS* in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.1 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 27 g/L solution of *tetrabutylammonium hydrogen sulfate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	80 → 40	20 → 60
30 - 35	40	60
35 - 40	40 → 80	60 → 20

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Relative retention With reference to bromperidol decanoate (retention time = about 24 min): impurity G = about 0.10; impurity L = about 0.15; impurity H = about 0.8; impurity A = about 0.89; impurity I = about 0.91; impurity B = about 0.96; haloperidol decanoate = about 0.98; impurity F = about 1.10; impurity C = about 1.15; impurity K = about 1.2; impurity E = about 1.23; impurity D = about 1.25.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to haloperidol decanoate and bromperidol decanoate.

Limits:

— *impurities A, B, C, D, E, F, G, H, I, J, K*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 30 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.450 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 57.46 mg of $C_{31}H_{41}BrFNO_3$.

STORAGE

Protected from light, at a temperature below 25 °C.

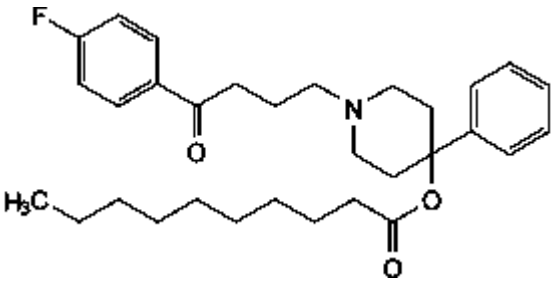
IMPURITIES

www.webofpharma.com

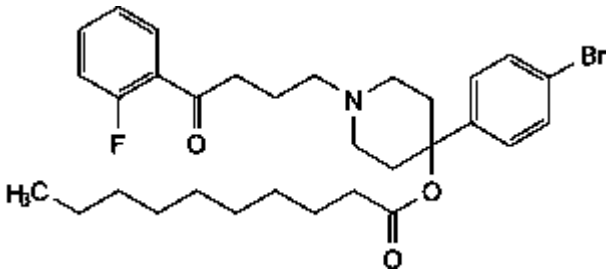
https://thuvienthuocngocanh.com/

Specified impurities A, B, C, D, E, F, G, H, I, J, K.

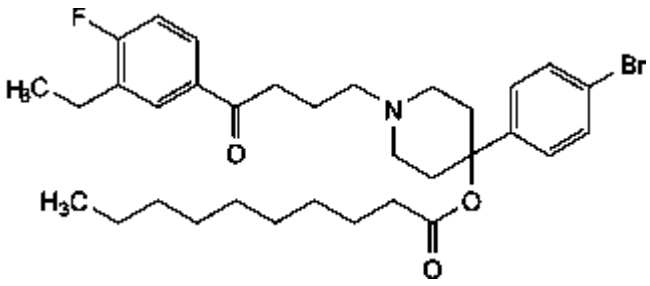
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) L.



A. 1-[4-(4-fluorophenyl)-4-oxobutyl]-4-phenylpiperidin-4-yl decanoate,



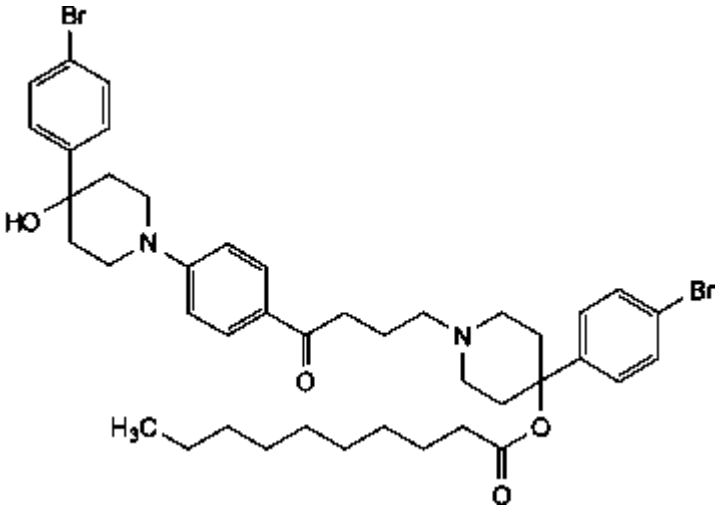
B. 4-(4-bromophenyl)-1-[4-(2-fluorophenyl)-4-oxobutyl]-piperidin-4-yl decanoate,



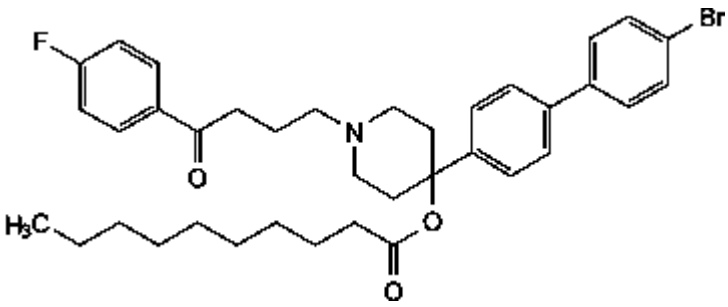
C. 4-(4-bromophenyl)-1-[4-(3-ethyl-4-fluorophenyl)-4-oxobutyl]-piperidin-4-yl decanoate,

www.webofpharma.com

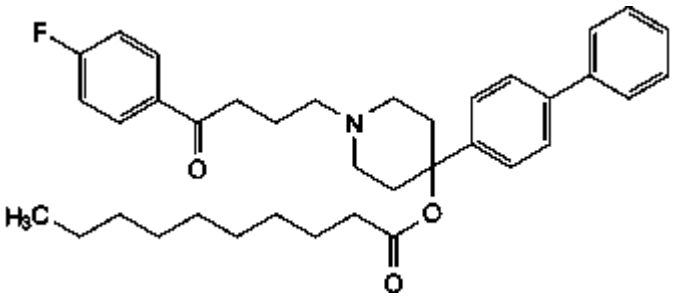
https://thuocngocanh.com/



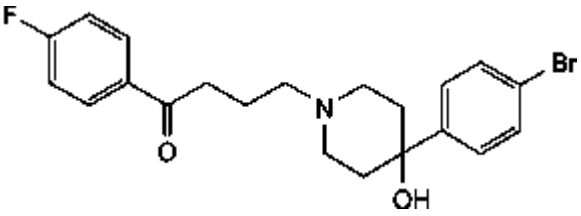
D. 4-(4-bromophenyl)-1-[4-[4-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]phenyl]-4-oxobutyl]piperidin-4-yl decanoate,



E. 4-(4′-bromobiphenyl-4-yl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl decanoate,



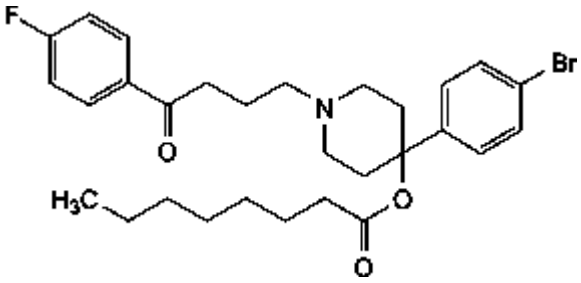
F. 4-(biphenyl-4-yl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl decanoate,



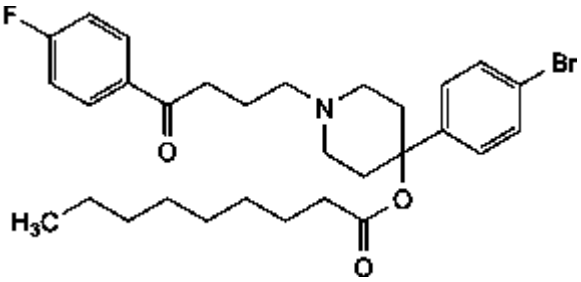
G. 4-[4-(4-bromophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one (bromperidol),

www.webofpharma.com

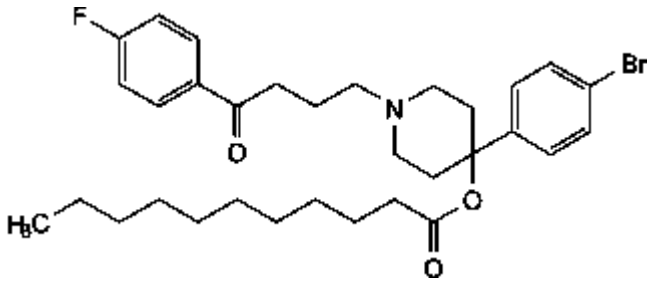
https://thuocngocanh.com/



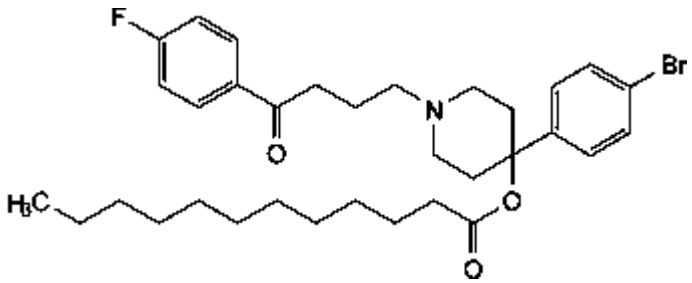
H. 4-(4-bromophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl octanoate,



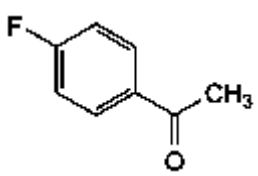
I. 4-(4-bromophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl nonanoate,



J. 4-(4-bromophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl undecanoate,



K. 4-(4-bromophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl dodecanoate,



L. 1-(4-fluorophenyl)ethanone.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products
Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

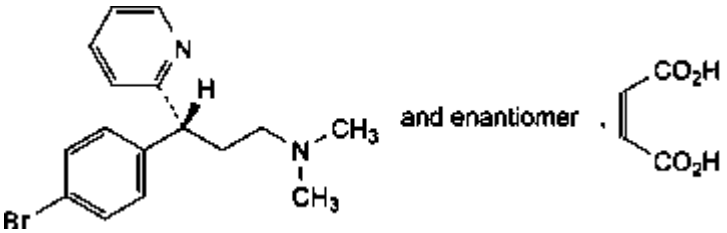
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Brompheniramine Maleate

General Notices

(Ph. Eur. monograph 0977)



$C_{20}H_{23}BrN_2O_4$ 435.3 *980-71-2*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

(3*RS*)-3-(4-Bromophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (*Z*)-butenedioate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, freely soluble in ethanol (96 per cent), in methanol and in methylene chloride.

IDENTIFICATION

First identification: C, F.

Second identification: A, B, D, E, F.

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 130 °C to 135 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 65 mg in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solution. Dilute 5.0 mL of this solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Spectral range 220-320 nm.

Absorption maximum At 265 nm.

Specific absorbance at the absorption maximum 190 to 210.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *brompheniramine maleate CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 56 mg of *maleic acid R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *anhydrous formic acid R*, *methanol R*, *di-isopropyl ether R* (3:7:20:70 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In a current of air for 5 min.

Detection Examine in ultraviolet light at 254 nm.

Results The chromatogram obtained with the test solution shows 2 clearly separated spots; the upper spot is similar in position and size to the spot in the chromatogram obtained with the reference solution.

E. To 0.15 g in a porcelain crucible add 0.5 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue in 10 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of bromides (2.3.1).

F. Optical rotation (see Tests).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 2.0 g in *methanol R* and dilute to 20 mL with the same solvent.

pH (*2.2.3*)

4.0 to 5.0.

Dissolve 0.20 g in 20 mL of *carbon dioxide-free water R*.

Optical rotation (*2.2.7*)

-0.20° to + 0.20° (measured in a 2 dm tube).

Dissolve 2.5 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Gas chromatography (*2.2.28*).

Test solution Dissolve 0.100 g of the substance to be examined in 10.0 mL of *methylene chloride R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 10.0 mL with *methylene chloride R*.

Reference solution (b) Dissolve 10 mg of *chlorphenamine maleate CRS* (impurity A) and 10 mg of *pheniramine maleate CRS* (impurity C) in *methylene chloride R* and dilute to 5 mL with the same solvent. To 2.5 mL of the solution add 2.5 mL of the test solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 0.5 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 1.0 mL/min.

Split ratio 1:5.

Temperature:

— *column*: 205 °C;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Injection 1 µL.

www.webofpharma.com

https://thuocngocanh.com/

Run time 1.2 times the retention time of brompheniramine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention With reference to brompheniramine (retention time = about 34 min): impurity C = about 0.4; impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and brompheniramine.

Limits:

— *impurities A, C*: for each impurity, not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.260 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 21.77 mg of $C_{20}H_{23}BrN_2O_4$.

STORAGE

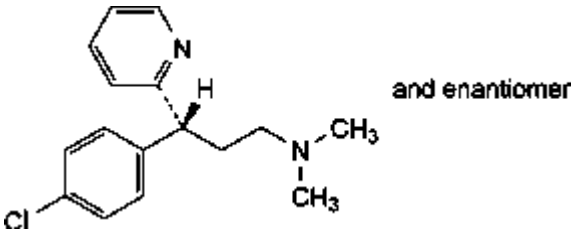
Protected from light.

IMPURITIES

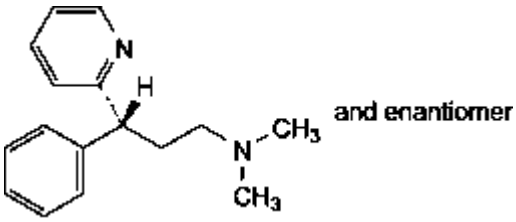
Specified impurities *A, C.*

www.webofpharma.com

https://thuvienthuocngocanh.com/



A. (3*RS*)-3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (chlorphenamine),



C. (3*RS*)-*N*,*N*-dimethyl-3-phenyl-3-(pyridin-2-yl)propan-1-amine (pheniramine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

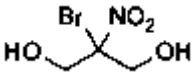
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bronopol

General Notices



$C_3H_6BrNO_4$ 200.0 *52-51-7*

Action and use

Antibacterial preservative.

DEFINITION

Bronopol is 2-bromo-2-nitropropane-1,3-diol. It contains not less than 99.0% and not more than 101.0% of $C_3H_6BrNO_4$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

White or almost white crystals or crystalline powder.

Freely soluble in *water* and in *ethanol (96%)*; slightly soluble in *glycerol* and in *liquid paraffin*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of bronopol *(RS 031)*.

B. Dissolve 0.1 g in 10 mL of *water*, add 10 mL of 7.5M *sodium hydroxide* and, carefully with constant stirring and cooling, 0.5 g of *nickel-aluminium alloy*. Allow the reaction to subside, filter and carefully neutralise with *nitric acid*. The resulting solution yields reaction A characteristic of *bromides*, Appendix VI.

C. *Melting point*, after drying over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa, about 130°, Appendix V A.

TESTS

Acidity or alkalinity

pH of a 1% w/v solution, 5.0 to 7.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

(1) 0.2% w/v of the substance being examined.

(2) Dilute a volume of solution (1) to produce a solution containing 0.0002% w/v of the substance being examined.

(3) 0.001% w/v each of *2-methyl-2-nitropropan-1,3-diol* and *tris(hydroxymethyl)nitromethane*.

(4) 0.0002% w/v each of 2-methyl-2-nitropropane-1,3-diol, 2-nitroethanol, sodium bromide and tris(hydroxymethyl)nitromethane and 0.2% w/v of the substance being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18 (2) is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 214 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for at least 3 times the retention time of the principal peak.

MOBILE PHASE

1 volume of a 10% v/v solution of *orthophosphoric acid*, 10 volumes of *acetonitrile* and 189 volumes of *water*, adjust the pH to 3.0 using 2M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution factor* between the peaks due to sodium bromide and tris(hydroxymethyl)nitromethane is at least 1.0;

the *resolution factor* between the peaks due to tris(hydroxymethyl)nitromethane and 2-nitroethanol is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-methyl-2-nitropropane-1,3-diol and tris(hydroxymethyl)nitromethane are not greater than the area of the corresponding peaks in the chromatogram obtained with solution (3) (0.5% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Sulfated ash

Not more than 0.1%, Appendix IX A.

Water

Not more than 0.5% w/w, Appendix IX C, Method I B. Use 5 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

In a flask fitted with a reflux condenser dissolve 0.4 g in 15 mL of *water* and add 15 mL of *7.5M sodium hydroxide*. Slowly, with caution, add 2 g of *nickel-aluminium alloy* through the reflux condenser, agitating the flask whilst cooling under running water. Allow the mixture to stand for 10 minutes and boil for 1 hour. Cool and filter under reduced pressure, washing the condenser, flask and residue with 150 mL of *water*. Combine the filtrate and washings, add 25 mL of *nitric acid* and 40 mL of *0.1M silver nitrate VS*, shake vigorously and titrate with *0.1M ammonium thiocyanate VS* using *ammonium iron(III) sulfate solution R2* as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of silver nitrate required. Each mL of *0.1M silver nitrate VS* is equivalent to 20.00 mg of $C_3H_6BrNO_4$.

STORAGE

Bronopol should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

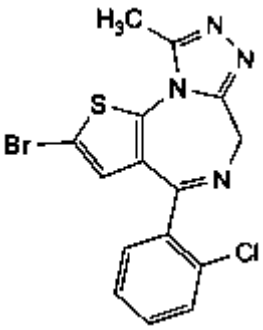
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Brotizolam

General Notices

(Ph. Eur. monograph 2197)



$C_{15}H_{10}BrClN_4S$ 393.7 *57801-81-7*

Action and use

Benzodiazepine.

Ph Eur

DEFINITION

2-Bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno-[3,2-*f*][1,2,4]-triazolo[4,3-*a*][1,4]diazepine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish powder.

Solubility

Practically insoluble in water, sparingly soluble or slightly soluble in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *brotizolam CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light and prepare the solutions immediately before use.*

Test solution Dissolve 50.0 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL of *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *brotizolam impurity B CRS* in 50 mL of *acetonitrile R*. Dilute 2 mL of this solution to 20 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 2 g/L solution of *sodium heptanesulfonate monohydrate R*;

— *mobile phase B*: mix 25 volumes of a 2 g/L solution of *sodium heptanesulfonate R* and 75 volumes of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	63	37
4 - 15	63 → 12	37 → 88

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 242 nm.

Injection 5 µL.

Relative retention With reference to brotizolam (retention time = about 7.4 min): impurity A = about 0.5; impurity B = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity B and brotizolam.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (2.4.4)

Maximum 100 ppm.

Dissolve 0.67 g in 20.0 mL of *methanol R*, mix and filter.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

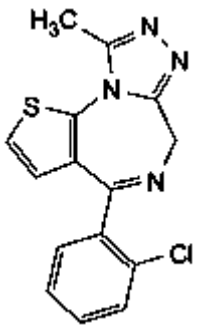
Dissolve 0.150 g in a mixture of 25 mL of *glacial acetic acid R* and 50 mL of *acetic anhydride R*. Titrate to the second point of inflexion with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 19.68 mg of $C_{15}H_{10}BrClN_4S$.

IMPURITIES

Specified impurities B.

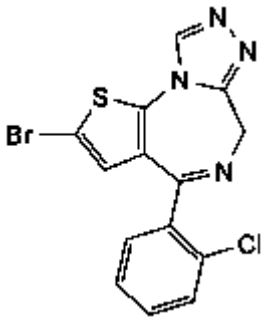
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



www.webofpharma.com

https://thuvienthuocngocanh.com/

A. 4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (desbromobrotizolam),



B. 2-bromo-4-(2-chlorophenyl)-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (desmethylbrotizolam).

Ph Eur

© Crown Copyright 2022

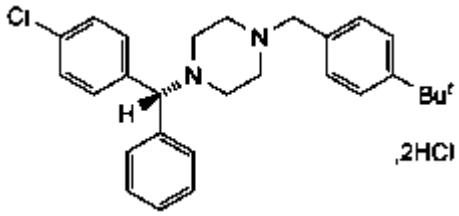
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buclizine Hydrochloride

General Notices



$C_{28}H_{33}ClN_2$,2HCl 506.0 *129-74-8*

Action and use

Histamine H_1 receptor antagonist; antiemetic.

DEFINITION

Buclizine Hydrochloride is (*RS*)-1-(4-*tert*-butylbenzyl)-4-(4-chlorobenzhydryl)piperazine dihydrochloride. It contains not less than 99.0% and not more than 100.5% of $C_{28}H_{33}ClN_2$,2HCl, calculated with reference to the dried substance.

CHARACTERISTICS

A white or slightly yellowish, crystalline powder.

Practically insoluble in *water*; sparingly soluble in *propane-1,2-diol*; very slightly soluble in *ethanol (96%)*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of buclizine hydrochloride *(RS 032)*.

B. A 0.25% w/v solution in *ethanol (50%)* yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using four solutions in the initial mobile phase containing (1) 0.0010% w/v of the substance being examined, (2) 0.50% w/v of the substance being examined, (3) 0.0010% w/v of *1,4-bis(4-chlorobenzhydryl)piperazine BPCRS* and (4) 0.50% w/v of *buclizine hydrochloride impurity standard BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic procedure may be carried out using a stainless steel column (20 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable). Use as the initial mobile phase *0.01M* *sodium heptanesulfonate* in a mixture of 55 volumes of *water* and 45 volumes of *acetonitrile* and as the final mobile phase *0.01M* *sodium heptanesulfonate* in a mixture of 20 volumes of *water* and 80 volumes of *acetonitrile*. Before use, adjust the pH of both the initial and final mobile phases to 4.0 with *1M* *orthophosphoric acid*. Carry out a linear gradient elution with a flow rate of 2 mL per minute for 30 minutes and maintain the final mobile phase for 10 minutes with the same flow rate. Use a detection wavelength of 230 nm.

The test is not valid unless the chromatogram obtained with solution (4) closely resembles the chromatogram supplied with *buclizine hydrochloride impurity standard BPCRS*.

In the chromatogram obtained with solution (2) the area of any peak corresponding to 1,4-bis(4-chlorobenzhydryl)-piperazine is not greater than the area of the peak obtained in the chromatogram with solution (3) and the area of any other *secondary peak* is not greater than the area of the peak in the chromatogram obtained with solution (1).

Loss on drying

When dried to constant weight at 100° to 105°, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.4 g and determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 25.30 mg of $C_{28}H_{33}ClN_2,2HCl$.

IMPURITIES

A. 1,4-bis(4-chlorobenzhydryl)piperazine,

B. 4-chlorobenzhydrol, 1-(4-chlorobenzhydryl)piperazine,

4-chlorobenzophenone.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

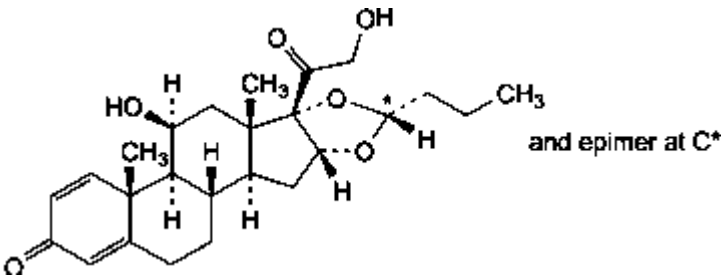
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Budesonide

General Notices

(Ph. Eur. monograph 1075)



$C_{25}H_{34}O_6$ 430.5 *51333-22-3*

Action and use

Glucocorticoid.

Preparations

Budesonide Aqueous Nasal Spray

Budesonide Inhalation Powder

Budesonide Inhalation Powder, pre-metered

Budesonide Nebuliser Suspension

Budesonide Pressurised Inhalation

Ph Eur

DEFINITION

Mixture of the C-22*S* (epimer A) and the C-22*R* (epimer B) epimers of 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison budesonide CRS.

B. Thin-layer chromatography (2.2.27).

Solvent mixture methanol R, methylene chloride R (10:90 *V/V*).

Test solution Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve 25 mg of budesonide CRS in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dissolve 12.5 mg of triamcinolone acetonide CRS in reference solution (a) and dilute to 5 mL with reference solution (a).

Plate TLC silica gel F_{254} plate R.

Mobile phase Add a mixture of 1.2 volumes of water R and 8 volumes of methanol R to a mixture of 15 volumes of ether R and 77 volumes of methylene chloride R.

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with alcoholic solution of sulfuric acid R; heat at 120 °C for 10 min or until the spots appear and allow to cool; examine the chromatograms in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

C. Dissolve about 2 mg in 2 mL of *sulfuric acid R*. Within 5 min a yellow colour develops. Within 30 min the colour changes to brown or reddish-brown. Cautiously add the solution to 10 mL of *water R* and mix. The colour fades and a clear solution remains.

D. Dissolve about 1 mg in 2 mL of a solution containing 2 g of *phosphomolybdic acid R* dissolved in a mixture of 10 mL of *dilute sodium hydroxide solution R*, 15 mL of *water R* and 25 mL of *glacial acetic acid R*. Heat for 5 min on a water-bath. Cool in iced water for 10 min and add 3 mL of *dilute sodium hydroxide solution R*. The solution is blue.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture *acetonitrile R*, *phosphate buffer solution pH 3.2 R* (32:68 *V/V*).

Test solution (a) Dissolve 50 mg of the substance to be examined in 15 mL of *acetonitrile R* and dilute to 50 mL with *phosphate buffer solution pH 3.2 R*.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in 15 mL of *acetonitrile R* and dilute to 50.0 mL with *phosphate buffer solution pH 3.2 R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *budesonide for system suitability CRS* (containing impurities A, D, G, K and L) in 1.5 mL of *acetonitrile R* and dilute to 5 mL with *phosphate buffer solution pH 3.2 R*.

Reference solution (c) Dissolve 25.0 mg of *budesonide CRS* in 15 mL of *acetonitrile R* and dilute to 50.0 mL with *phosphate buffer solution pH 3.2 R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: *anhydrous ethanol R*, *acetonitrile R*, *phosphate buffer solution pH 3.2 R* (2:32:68 *V/V/V*);

— *mobile phase B*: *acetonitrile R*, *phosphate buffer solution pH 3.2 R* (50:50 *V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 38	100	0
38 - 50	100 → 0	0 → 100
50 - 60	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *budesonide for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, D, G, K and L.

Relative retention With reference to budesonide epimer B (retention time = about 17 min): impurity A = about 0.1; epimers of impurity D = about 0.63 and 0.67; impurity L = about 0.95; epimers of impurity G = about 1.2 and 1.3; epimers of impurity K = about 2.9 and 3.0.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the 1st of the 2 peaks due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to budesonide epimer A (the 2nd of the 2 principal peaks); and minimum 3, where H_p = height above the baseline of the peak due to impurity L and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to budesonide epimer B (the 1st of the 2 principal peaks).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.8; impurity K = 1.3;

— *impurities A, L*: for each impurity, not more than twice the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities D, K*: for each impurity, for the sum of the areas of the 2 epimer peaks, not more than twice the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each individual peak, not more than the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.5 times the sum of the areas of the 2 peaks due to the budesonide epimers in the chromatogram obtained with reference solution (a) (0.05 per cent).

Epimer A

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 21	100	0
21 - 22	100 → 0	0 → 100
22 - 31	0	100

Injection 20 µL of test solution (b) and reference solutions (b) and (c).

Retention time Budesonide epimer B = about 17 min; budesonide epimer A = about 19 min.

System suitability:

— *resolution*: minimum 1.5 between the 2 principal peaks (budesonide epimers A and B) in the chromatogram obtained with reference solution (c);

— *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity L and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to budesonide epimer B (the 1st of the 2 principal peaks) in the chromatogram obtained with reference solution (b).

Limit:

— *epimer A*: 40.0 per cent to 51.0 per cent of the sum of the areas of the 2 peaks due to the budesonide epimers.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (2.2.29). Examine the chromatograms obtained in the test for epimer A.

Calculate the percentage content of $C_{25}H_{34}O_6$ from the sum of the areas of the 2 peaks due to the budesonide epimers and the declared content of *budesonide CRS*.

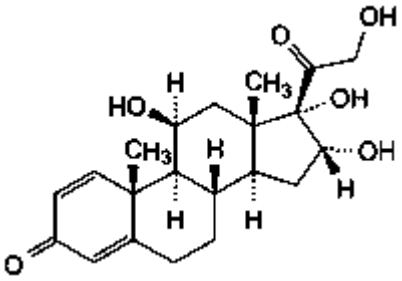
IMPURITIES

www.webofpharma.com

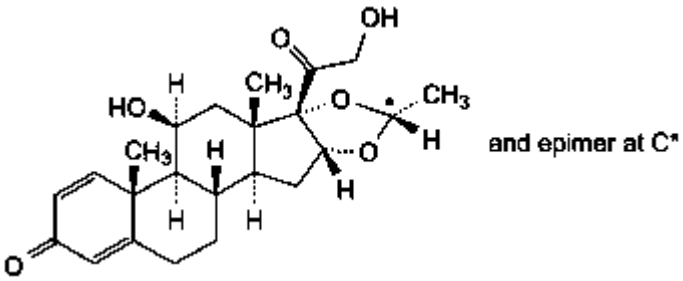
https://thuocngocanh.com/

Specified impurities A, D, K, L.

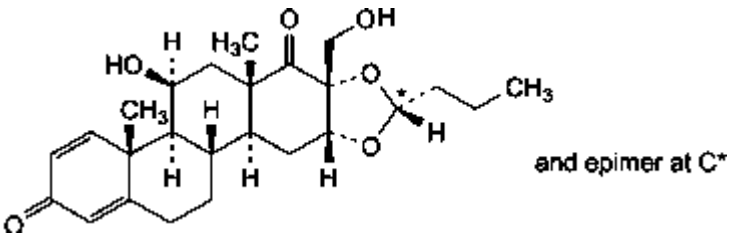
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, E, F, G, H, I, J.



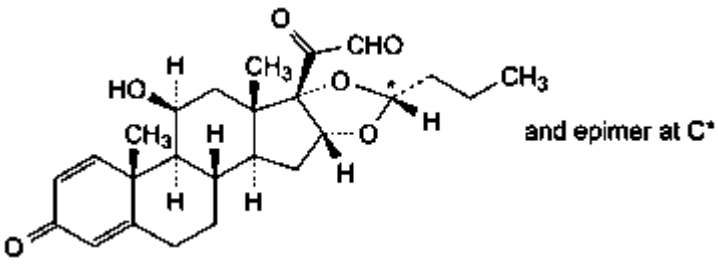
A. 11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione,



B. 16α,17-[(1*RS*)-ethylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione,



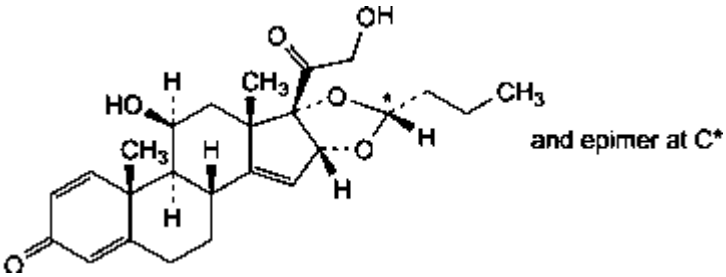
C. 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β-hydroxy-17-(hydroxymethyl)-*D*-homoandrosta-1,4-diene-3,17a-dione,



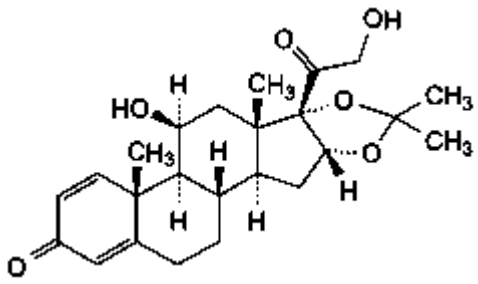
D. 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-al,

www.webofpharma.com

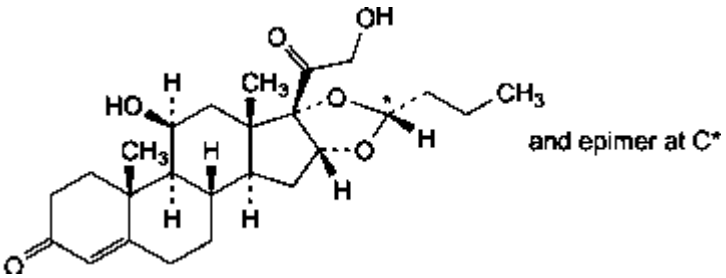
https://thuocngocanh.com/



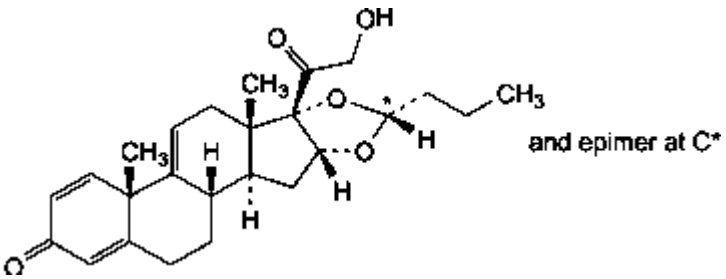
E. 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4,14-triene-3,20-dione,



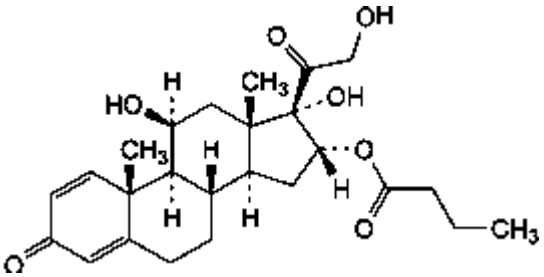
F. 16α,17-[1-methylethylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione,



G. 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregn-4-ene-3,20-dione.



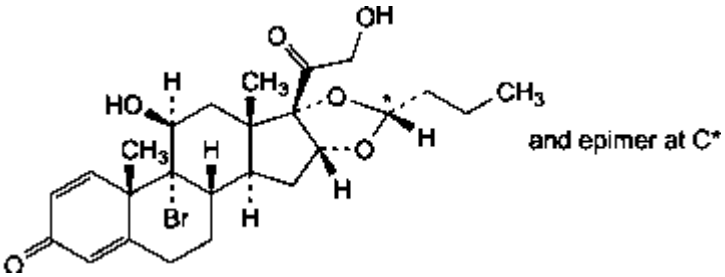
H. 16α,17-[(1*RS*)-butylidenebis(oxy)]-21-hydroxypregna1,4,9(11)-triene-3,20-dione,



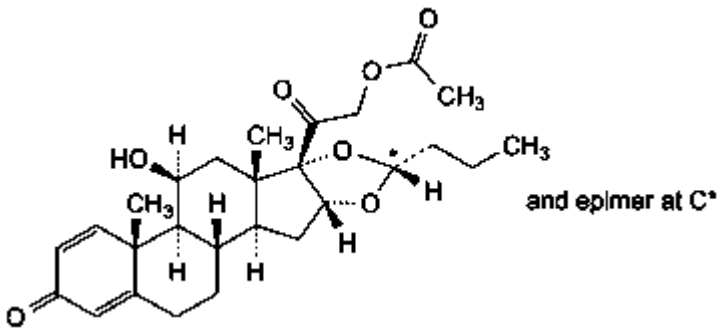
I. 11β,17,21-trihydroxy-3,20-dioxopregna-1,4-dien-16α-yl butanoate,

www.webofpharma.com

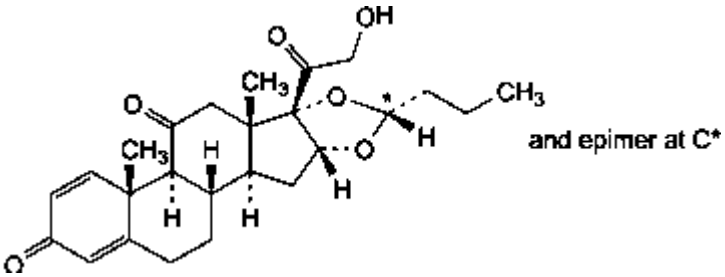
https://thuocngocanh.com/



J. 16α,17-[(1*RS*)-butylidenebis(oxy)]-9α-bromo-11β,21-dihydroxypregna-1,4-diene-3,20-dione,



K. 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione-21-acetate,



L. 16α,17-[(1*RS*)-butylidenebis(oxy)]-21-hydroxypregna-1,4-diene-3,11,20-trione.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Budesonide Aqueous Nasal Spray

General Notices

Action and use

Glucocorticoid.

DEFINITION

Budesonide Aqueous Nasal Spray is an aqueous suspension of Budesonide in a suitable container fitted with an appropriate nasal delivery system.

The nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of budesonide, $C_{25}H_{34}O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dilute a quantity of the nasal spray with sufficient *water* to produce a solution containing 0.002% w/v of Budesonide and filter. The *light absorption* of the resulting solution, Appendix II B, in the range 200 nm to 350 nm exhibits a maximum only at 247 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 5.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

Solvent A 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

(1) To a quantity of the nasal spray containing 2 mg of Budesonide add 3.4 mL of *acetonitrile*. Mix with the aid of ultrasound and add sufficient *phosphate buffer solution pH 3.2* to produce 10 mL and filter.

(2) Dilute 1 volume of solution (1) to 50 volumes in solvent A.

(3) 0.01% w/v of *budesonide impurity standard BPCRS* in solvent A.

(4) Dilute 1 volume of solution (2) to 20 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

Mobile phase B Equal volumes of *acetonitrile* and *phosphate buffer solution pH 3.2*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-38	100	0	isocratic
38-50	100→0	0→100	linear gradient
50-60	0	100	isocratic
60-61	0→100	100→0	linear gradient
61-70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to budesonide epimer B (retention time about 17 minutes) is epimer A, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5;

the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *budesonide impurity standard BPCRS*;

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* of each of the peaks due to epimer A and epimer B is at least 10.

LIMITS

Identify any peaks (2 epimer peaks) due to impurity D in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (3) and multiply the sum of the areas of these peaks by 1.8.

In the chromatogram obtained with solution (1):

the area of any peak due to Impurity D is not greater than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (2%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (4) (0.1%).

Epimer A

In the chromatogram obtained with solution (1), as described under Assay, the content of epimer A (second peak) is 40.0% to 51.0% of the sum of the areas of the two epimer peaks of budesonide.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) To a quantity of the nasal spray containing 1 mg of Budesonide add 3.4 mL of *acetonitrile*. Mix with the aid of ultrasound, add sufficient *phosphate buffer solution pH 3.2* to produce 10 mL and filter.
(2) 0.01% w/v of *budesonide BPCRS* in solvent A (as described under Related substances).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{34}O_6$ in the nasal spray from the sum of the areas of the two budesonide epimer peaks and using the declared content of $C_{25}H_{34}O_6$ in *budesonide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Budesonide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Budesonide Inhalation Powder

General Notices

Budesonide Powder for Inhalation, metered dose powder inhaler

Action and use

Glucocorticoid.

DEFINITION

Budesonide Inhalation Powder consists of Budesonide in *microfine powder* or aerodynamically equivalent,either alone or combined with a suitable carrier. It is administered by a dry-powder inhaler.

The inhalation powder complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of budesonide, $C_{25}H_{34}O_6$

80.0 to 120.0% of the stated amount.

IDENTIFICATION

A. Dilute a quantity of the inhalation powder with sufficient *water* to produce a solution containing 0.002% w/v of Budesonide and filter. The *light absorption* of the resulting solution, Appendix II B, in the range 200 nm to 350 nm exhibits a maximum only at 247 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

C. *For products containing lactose* disperse 0.25 g of the inhalation powder in 5 mL of *water*. Add 5 mL of 6M *ammonia* and heat in a water bath at 80° for 10 minutes. An orange-red colour is produced.

TESTS

Uniformity of delivered dose

www.webofpharma.com

https://thuocngocanh.com/

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

Solvent A 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient solvent A to produce a solution containing 0.001% w/v of Budesonide.
(2) 0.001% w/v of *budesonide BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the amount of budesonide, $C_{25}H_{34}O_6$, per delivered dose using the declared content of $C_{25}H_{34}O_6$ in *budesonide BPCRS*. Repeat the procedure as described for reservoir systems under Inhalation Powders, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

Prepare a mixture of 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2* (solvent A).

(1) Dissolve a quantity of the inhalation powder containing 2 mg of Budesonide in 3.4 mL of *acetonitrile*. Mix with the aid of ultrasound, add sufficient *phosphate buffer solution pH 3.2* to produce 10 mL and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with solvent A.
(3) Dilute 1 volume of solution (2) to 10 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).
(b) Use gradient elution and the mobile phase described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

Mobile phase B Equal volumes of *acetonitrile* and *phosphate buffer solution pH 3.2*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-38	100	0	isocratic
38-50	100→0	0→100	linear gradient
50-60	0	100	isocratic
60-61	0→100	100→0	linear gradient
61-70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to budesonide epimer B (retention time about 17 minutes) is epimer A, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5;

in the chromatogram obtained with solution (3), the *signal-to-noise ratio* of each of the peaks due to epimer A and epimer B is at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 3 times the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (3) (0.05%).

Epimer A

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1), as described under Uniformity of delivered dose, the content of epimer A (second peak) is 40.0% to 51.0% of the sum of the areas of the two epimer peaks of budesonide.

ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Budesonide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Budesonide Inhalation Powder, pre-metered

General Notices

Budesonide Powder for Inhalation, pre-dispensed units

Action and use

Glucocorticoid.

DEFINITION

Budesonide Inhalation Powder, pre-metered consists of Budesonide in *microfine powder* either alone or combined with a suitable carrier. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, pre-metered complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of budesonide, $C_{25}H_{34}O_6$

When supplied as disks, 90.0 to 110.0% of the stated amount per pre-metered unit. When supplied as capsules, 80.0 to 120.0% of the stated amount per pre-metered unit.

IDENTIFICATION

A. Dilute a quantity of the powder, with sufficient *water* to produce a solution containing 0.002% w/v of Budesonide and filter. The *light absorption* of the resulting solution, Appendix II B, in the range 200 nm to 350 nm exhibits a maximum only at 247 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

C. *For products containing lactose* disperse 0.25 g of the powder for inhalation in 5 mL of *water*. Add 5 mL of 6M *ammonia* and heat in a water bath at 80° for 10 minutes. An orange-red colour is produced.

TESTS

Uniformity of delivered dose

www.webofpharma.com

https://thuocngocanh.com/

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

Solvent A 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient solvent A to produce a solution containing 0.001% w/v of Budesonide.
(2) 0.001% w/v of *budesonide BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the amount of budesonide, $C_{25}H_{34}O_6$, per delivered dose inhalation from the sum of the areas of the two budesonide epimer peaks and using the declared content of $C_{25}H_{34}O_6$ in *budesonide BPCRS*. Repeat the procedure as described for pre-metered systems under Inhalation Powders, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

Prepare a mixture of 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2* (solvent A).

(1) Dissolve a quantity of the powder, containing 2 mg of Budesonide in 3.4 mL of *acetonitrile*. Mix with the aid of ultrasound, add sufficient *phosphate buffer solution pH 3.2* to produce 10 mL and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with solvent A.
(3) Dilute 1 volume of solution (2) to 10 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

Mobile phase B Equal volumes of *acetonitrile* and *phosphate buffer solution pH 3.2*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-38	100	0	isocratic
38-50	100→0	0→100	linear gradient
50-60	0	100	isocratic
60-61	0→100	100→0	linear gradient
61-70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to budesonide epimer B (retention time about 17 minutes) is epimer A, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5;

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 3 times the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (3) (0.05%).

Epimer A

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1), as described under Uniformity of delivered dose, the content of epimer A (second peak) is 40.0% to 51.0% of the sum of the areas of the two epimer peaks of budesonide.

ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Budesonide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Budesonide Nebuliser Suspension

General Notices

Action and use

Glucocorticoid.

DEFINITION

Budesonide Nebuliser Suspension is a suspension of Budesonide in a suitable vehicle, intended to be converted into aerosols by a nebuliser.

The nebuliser suspension complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The active substance delivery rate and the total active substance delivered are determined using the methods described in Appendix XII C. 8. Preparations for Nebulisation: Characterisation. Where justified and authorised, a different apparatus and procedure may be used.

The particle-size distribution is determined using an apparatus and procedure described in Appendix XII C. 8. Preparations for Nebulisation: Characterisation. Where justified and authorised, a different apparatus and procedure may be used.

Content of budesonide, $C_{25}H_{34}O_6$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a quantity of the nebuliser suspension being examined with sufficient *water* to produce a solution containing 0.002% w/v of Budesonide and filter. The *light absorption* of the resulting solution, Appendix II B, in the range 200 nm to 350 nm exhibits a maximum only at 247 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 5.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

www.webofpharma.com

https://thuocngocanh.com/

Solvent A 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

(1) To a quantity of the nebuliser suspension containing 2 mg of Budesonide add 3.4 mL of *acetonitrile*. Mix with the aid of ultrasound, add sufficient *phosphate buffer solution pH 3.2* to produce 10 mL, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 200 volumes with solvent A.

(3) Dilute 1 volume of solution (2) to 10 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

Mobile phase B Equal volumes of *acetonitrile* and *phosphate buffer solution pH 3.2*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-38	100	0	isocratic
38-50	100→0	0→100	linear gradient
50-60	0	100	isocratic
60-61	0→100	100→0	linear gradient
61-70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to budesonide epimer B (retention time about 17 minutes) is epimer A, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5;

in the chromatogram obtained with solution (3), the *signal-to-noise ratio* of each of the peaks due to epimer A and epimer B is at least 10.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 3 times the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (3) (0.05%).

Epimer A

In the chromatogram obtained with solution (1), as described under Assay, the content of epimer A (second peak) is 40.0% to 51.0% of the sum of the areas of the two epimer peaks of budesonide.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) To a quantity of the nebuliser suspension containing 1 mg of Budesonide add 3.4 mL of *acetonitrile*. Mix with the aid of ultrasound, add sufficient *phosphate buffer solution pH 3.2* to produce 10 mL and filter.
(2) 0.01% w/v of *budesonide BPCRS* in solvent A (as described under Related substances).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{34}O_6$ in the nebuliser suspension from the sum of the areas of the two budesonide epimer peaks and using the declared content of $C_{25}H_{34}O_6$ in *budesonide BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

Budesonide Nebuliser Suspension should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Budesonide.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Budesonide Pressurised Inhalation

General Notices

Action and use

Glucocorticoid.

DEFINITION

Budesonide Pressurised Inhalation is a suspension of Budesonide in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of budesonide, $C_{25}H_{34}O_6$

80.0 to 120.0% of the amount stated to be delivered by actuation of the valve.

IDENTIFICATION

A. Dilute a quantity of the pressurised inhalation with sufficient *water* to produce a solution containing 0.002% w/v of Budesonide and filter. The *light absorption* of the resulting solution, Appendix II B, in the range 200 nm to 350 nm exhibits a maximum only at 247 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

Solvent A 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

(1) Freeze the pressurised container and carefully open the canister. Dissolve a quantity of the frozen contents containing 2 mg of Budesonide in 3.4 mL of *acetonitrile*. Mix with the aid of ultrasound and add sufficient *phosphate buffer solution pH 3.2* to produce 10 mL

www.webofpharma.com

https://thuvienthuocngocanh.com/

and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with solvent A.

(3) Dilute 1 volume of solution (2) to 10 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

Mobile phase B Equal volumes of *acetonitrile* and *phosphate buffer solution pH 3.2*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-38	100	0	isocratic
38-50	100→0	0→100	linear gradient
50-60	0	100	isocratic
60-61	0→100	100→0	linear gradient
61-70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to budesonide epimer B (retention time about 17 minutes) is epimer A, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5;

in the chromatogram obtained with solution (3), the *signal-to-noise ratio* of each of the peaks due to epimer A and epimer B is at least 10.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any *secondary peak* is not greater than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 3 times the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (3) (0.05%).

Epimer A

In the chromatogram obtained with solution (1), as described under Assay, the content of epimer A (second peak) is 40.0% to 51.0% of the sum of the areas of the two epimer peaks of budesonide.

ASSAY

Protect the solutions from light.

Determine the content of active ingredient delivered by the first 10 successive combined actuations of the valve after priming. Carry out the procedure for Content of active ingredient delivered by actuation of the valve described under Appendix XII C, beginning at the words 'Remove the pressurised container from the actuator ...' and ending at the words '... to the volume specified in the monograph', using 32 mL of *acetonitrile* in the vessel. Transfer the combined solution and washings obtained from the set of 10 combined actuations to a flask so that, on dilution to volume with appropriate amounts of *acetonitrile* and *phosphate buffer solution pH 3.2*, the final solution contains 0.002% w/v of Budesonide in solvent A, as described under Related substances (solution A). Determine the content of active ingredient in the 10 combined actuations using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Solution A.
(2) 0.002% w/v of *budesonide BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *ethanol*, 34 volumes of *acetonitrile* and 66 volumes of *phosphate buffer solution pH 3.2*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to epimer B and epimer A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{34}O_6$ in the pressurised inhalation from the sum of the areas of the two budesonide epimer peaks and using the declared content of $C_{25}H_{34}O_6$ in *budesonide BPCRS*.

Determine the content of active ingredient a second and third time by repeating the procedure on the middle 10 and on the last 10 successive combined actuations of the valve, as estimated from the number of deliveries available from the container as stated on the label. For each of the three determinations the average content of $C_{25}H_{34}O_6$ delivered by a single actuation of the valve is within the limits stated under Content of budesonide.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Budesonide.

© Crown Copyright 2022

www.webofpharma.com

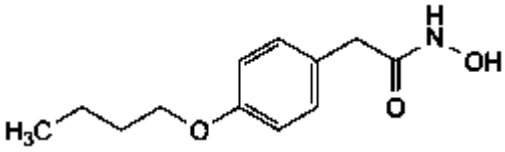
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bufexamac

General Notices

(Ph. Eur. monograph 1179)



$C_{12}H_{17}NO_3$ 223.3 *2438-72-4*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

2-(4-Butoxyphenyl)-*N*-hydroxyacetamide.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in dimethylformamide, slightly soluble in ethyl acetate and in methanol.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 20 mg in *methanol R* and dilute to 20 mL with the same solvent. Dilute 1 mL of the solution to 50 mL with *methanol R*.

Spectral range 210-360 nm.

Absorption maxima At 228 nm, 277 nm and 284 nm.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *bufexamac CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *bufexamac CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *salicylic acid R* in reference solution (a) and dilute to 5 mL with the same solution.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *dioxan R*, *toluene R* (4:20:90 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) Dilute 5.0 mL of the test solution to 25.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 5 mg of *bufexamac CRS*, 5 mg of *bufexamac impurity A CRS*, 5 mg of *bufexamac impurity B CRS*, 5 mg of *bufexamac impurity C CRS* and 5 mg of *bufexamac impurity D CRS* in mobile phase A and dilute to 10.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 30 volumes of a 1.4 g/L solution of *dipotassium hydrogen phosphate R* and 70 volumes of *methanol R*, then adjust to pH 3.6 with *dilute phosphoric acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 13	100 → 70	0 → 30
13 - 40	70	30

Flow rate 1 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to bufexamac (retention time = about 5.7 min): impurity D = about 1.3; impurity A = about 1.8; impurity B = about 3.0; impurity C = about 5.4.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to bufexamac and impurity D.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *dimethylformamide R*. Titrate with *0.1 M lithium methoxide*, determining the end-point potentiometrically (2.2.20).

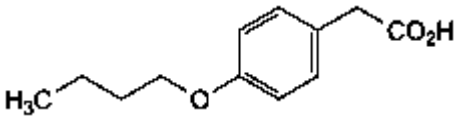
1 mL of *0.1 M lithium methoxide* is equivalent to 22.33 mg of $C_{12}H_{17}NO_3$.

STORAGE

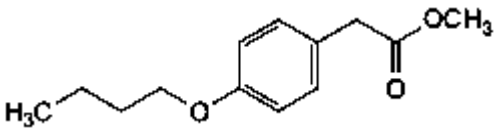
Protected from light.

IMPURITIES

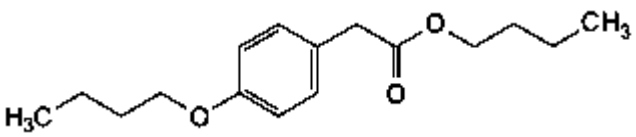
Specified impurities *A, B, C, D.*



A. 2-(4-butoxyphenyl)acetic acid,



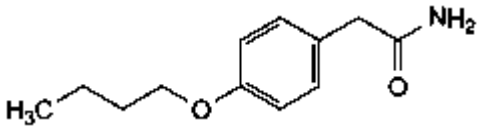
B. methyl 2-(4-butoxyphenyl)acetate,



C. butyl 2-(4-butoxyphenyl)acetate,

www.webofpharma.com

https://thuocngocanh.com/



D. 2-(4-butoxyphenyl)acetamide.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buffered Cream

General Notices

DEFINITION

Emulsifying Ointment	300 g
Disodium Hydrogen Phosphate Dodecahydrate	25 g
Citric Acid Monohydrate	5 g
Chlorocresol	1 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 g

If another antimicrobial preservative replaces Chlorocresol in this formulation, the suitability of the Cream as a diluent should be confirmed before use.

Extemporaneous preparation

Melt the Emulsifying Ointment with the aid of gentle heat. In a vessel that can be closed, heat about 650 g of Purified Water to about 60°; add the Chlorocresol and, when it melts, vigorously shake the closed vessel to effect dissolution. Dissolve the Disodium Hydrogen Phosphate Dodecahydrate and the Citric Acid Monohydrate in the chlorocresol solution. Add the aqueous phase to the melted ointment when both are at about 60°. Stir gently until cool, add sufficient Purified Water to produce 1000 g and mix.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

TESTS

Acidity

pH, 5.7 to 6.3, determined directly on the cream, Appendix V L.

STORAGE

If Buffered Cream is kept in aluminium tubes, their inner surfaces should be coated with a suitable lacquer.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

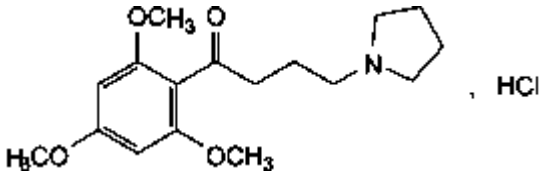
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buflomedil Hydrochloride

General Notices

(Ph. Eur. monograph 1398)



$C_{17}H_{26}ClNO_4$ 343.9 *35543-24-9*

Action and use

Vasodilator.

Ph Eur

DEFINITION

4-(Pyrrolidin-1-yl)-1-(2,4,6-trimethoxyphenyl)butan-1-one hydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, microcrystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), very slightly soluble in acetone.

mp

About 195 °C, with decomposition.

IDENTIFICATION

First identification: B, D.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25.0 mg in ethanol (96 per cent) R and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with ethanol (96 per cent) R.

Spectral range 220-350 nm.

Absorption maximum At 275 nm.

Specific absorbance at the absorption maximum 143 to 149.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison buflomedil hydrochloride CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 40 mg of the substance to be examined in methanol R and dilute to 2 mL with the same solvent.

Reference solution Dissolve 40 mg of buflomedil hydrochloride CRS in methanol R and dilute to 2 mL with the same solvent.

Plate TLC silica gel F_{254} plate R.

Mobile phase triethylamine R, 2-propanol R, toluene R (5:50:50 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in carbon dioxide-free water R and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

www.webofpharma.com

https://thuocngocanh.com/

pH (*2.2.3*)

5.0 to 6.5 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 0.5 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *buflomedil impurity B CRS* in the mobile phase, add 0.5 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *buflomedil for peak identification CRS* (containing impurities A and C) in 1.0 mL of reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 45 volumes of *acetonitrile R1* and 55 volumes of a 9.25 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Run time Twice the retention time of buflomedil.

Identification of impurities Use the chromatogram supplied with *buflomedil for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

Relative retention With reference to buflomedil (retention time = about 5 min): impurity B = about 0.6; impurity C = about 0.7; impurity A = about 1.5.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity B and impurity C.

Limits:

https://thuocngocanh.com/

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

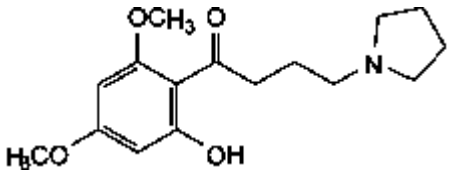
ASSAY

Dissolve 0.300 g in 15 mL of *anhydrous acetic acid R* and add 35 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

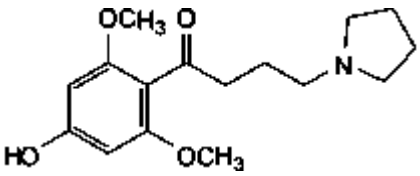
1 mL of *0.1 M perchloric acid* is equivalent to 34.39 mg of $C_{17}H_{26}ClNO_4$.

IMPURITIES

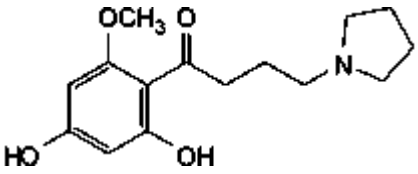
Specified impurities *A, B, C.*



A. 1-(2-hydroxy-4,6-dimethoxyphenyl)-4-(pyrrolidin-1-yl)butan-1-one,



B. 1-(4-hydroxy-2,6-dimethoxyphenyl)-4-(pyrrolidin-1-yl)butan-1-one,



www.webofpharma.com

https://thietbiuocngocanh.com/

C. 1-(2,4-dihydroxy-6-methoxyphenyl)-4-(pyrrolidin-1-yl)butan-1-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

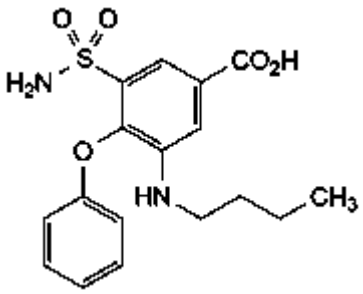
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bumetanide

General Notices

(Ph. Eur. monograph 1076)



$C_{17}H_{20}N_2O_5S$ 364.4 *28395-03-1*

Action and use

Loop diuretic.

Preparations

Bumetanide Injection

Bumetanide Oral Solution

Bumetanide and Potassium Prolonged-release Tablets

Bumetanide Tablets

Ph Eur

DEFINITION

3-(Butylamino)-4-phenoxy-5-sulfamoylbenzoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Practically insoluble in water, soluble in acetone and in ethanol (96 per cent), slightly soluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison bumetanide CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.1 g in a 6 g/L solution of potassium hydroxide R and dilute to 20 mL with the same solution.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of bumetanide impurity A CRS and 2 mg of bumetanide impurity B CRS in the mobile phase and dilute to 10 mL with the mobile phase. Dilute 1 mL of this solution to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped extra-dense bonded octylsilyl silica gel for chromatography R (3.5 µm).

Mobile phase Mix 70 volumes of methanol R, 25 volumes of water for chromatography R and 5 volumes of a 27.2 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 7.0 with a 280 g/L solution of potassium hydroxide R; add tetrahexylammonium bromide R to this mixture to obtain a concentration of 2.17 g/L.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 10 µL.

Run time 5 times the retention time of bumetanide.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to bumetanide (retention time = about 6 min): impurity B = about 0.4; impurity A = about 0.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities B and A.

Calculation of percentage contents:

— for each impurity, use the concentration of bumetanide in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of *alcohol R*. Add 0.1 mL of *phenol red solution R*. Titrate with *0.1 M sodium hydroxide* until a violet-red colour is obtained. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 36.44 mg of $C_{17}H_{20}N_2O_5S$.

STORAGE

Protected from light.

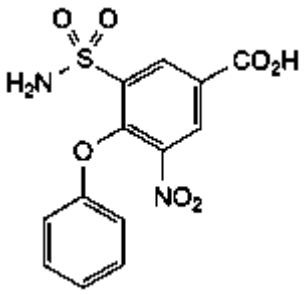
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

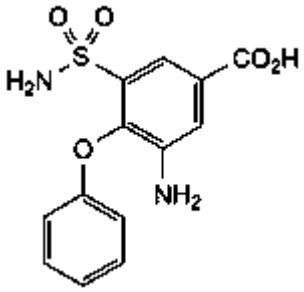
www.webofpharma.com

https://thuocngocanh.com/

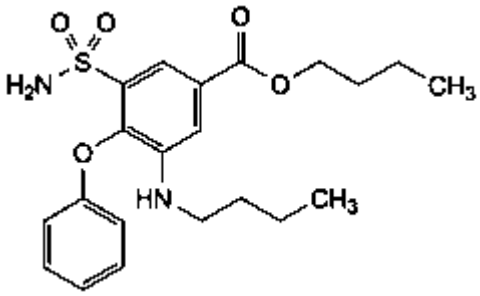
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.



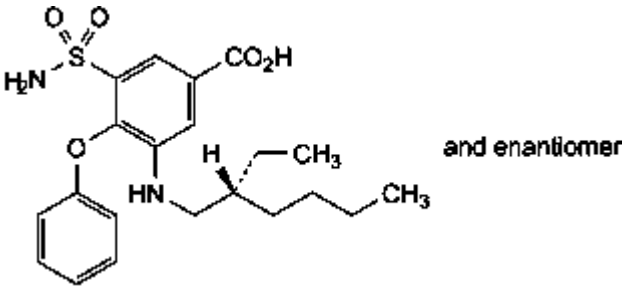
A. 3-nitro-4-phenoxy-5-sulfamoylbenzoic acid,



B. 3-amino-4-phenoxy-5-sulfamoylbenzoic acid,



C. butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate,



D. 3-[[(2*RS*)-2-ethylhexyl]amino]-4-phenoxy-5-sulfamoylbenzoic acid.

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bumetanide and Potassium Prolonged-release Tablets

General Notices

Bumetanide and Prolonged-release Potassium Tablets

Bumetanide and Potassium Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Loop diuretic.

DEFINITION

Bumetanide and Potassium Prolonged-release Tablets contain Bumetanide and Potassium Chloride. They are formulated so that the Potassium Chloride is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Potassium Chloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bumetanide, $C_{17}H_{20}N_2O_5S$

92.5 to 107.5% of the stated amount.

Content of potassium chloride, KCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the test for Related substances the spot in the chromatogram obtained with solution (1) is similar in position, size and intensity to the spot in the chromatogram obtained with solution (2).

B. Examine the filtrate obtained in the test for Uniformity of content by *fluorescence spectrophotometry*, Appendix II E, using an excitation wavelength of 350 nm. The solution emits light at 445 nm.

C. Dissolve a quantity of the powdered tablets containing 0.1 g of Potassium Chloride as completely as possible in 2 mL of *water* and filter. The filtrate yields reaction A characteristic of *potassium salts*, Appendix VI.

D. Dissolve a quantity of the powdered tablets containing 0.02 g of Potassium Chloride as completely as possible in 2 mL of *water* and filter. The filtrate yields reaction A characteristic of *chlorides*, Appendix VI.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Dissolution

For bumetanide

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *water* and rotate the paddle at 100 revolutions per minute. Withdraw a sample of 10 mL of the medium, filter and measure the *fluorescence*, Appendix II E, using an excitation wavelength of 350 nm and an emission wavelength of 445 nm and *water* in the reference cell. Measure the *fluorescence* of a 0.04% w/v solution of *bumetanide BPCRS* in *ethanol (96%)* diluted to a suitable concentration with *water* under the same conditions and calculate the total content of $C_{17}H_{20}N_2O_5S$ in the medium from the fluorescences obtained and from the declared content of $C_{17}H_{20}N_2O_5S$ in *bumetanide BPCRS*.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a high-performance silica gel F_{254} plate (Merck 5629 plates are suitable) and a mixture of 2.5 volumes of *methanol*, 10 volumes of *glacial acetic acid*, 10 volumes of *cyclohexane* and 80 volumes of *chloroform* as the mobile phase but allowing the solvent front to ascend 8 cm above the line of application. Apply separately to the plate 10 µL of each of solutions (1) and (2) and 5 µL of solution (3). For solution (1) add 10 mL of a 0.1% w/v solution of *citric acid* to a number of whole tablets containing, in total, 1 mg of Bumetanide, shake for 10 minutes, remove and discard the cores, extract the solution with two 20-mL quantities of *ether*, evaporate the combined extracts to dryness under reduced pressure and dissolve the residue in 0.5 mL of *ethyl acetate*. For solution (2) add 2 mL of a 0.20% w/v solution of *bumetanide BPCRS* in *ethyl acetate* to 10 mL of a 0.1% w/v solution of *citric acid*, shake for 15 minutes, centrifuge and use the ethyl acetate layer. For solution (3) mix 1 mL of a 0.20% w/v solution of *3-amino-4-phenoxy-5-sulfamoylbenzoic acid BPCRS* in *ethyl acetate* and 1 mL of a 0.20% w/v solution of *bumetanide BPCRS* in *ethyl acetate*, add sufficient *ethyl acetate* to produce 100 mL, add 2 mL of this solution to 10 mL of a 0.1% w/v solution of *citric acid*, shake for 15 minutes and use the ethyl acetate layer. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (365 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) corresponding to 3-amino-4-phenoxy-5-sulfamoylbenzoic acid is not more intense than the corresponding spot in the chromatogram obtained with solution (3) (0.5%) and any other *secondary spot* is not more intense than the spot due to bumetanide in the chromatogram obtained with solution (3) (0.5%).

Uniformity of content

Tablets containing less than 2 mg of Bumetanide comply with the requirements stated below. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake one tablet in 0.5 mL of *methanol* for 3 minutes, add 9 mL of the mobile phase and shake for 30 minutes. Filter to remove the tablet core, add sufficient of the mobile phase to produce 10 mL, centrifuge for 15 minutes and use the supernatant liquid. If the supernatant liquid is cloudy, filter through a 0.45-µm membrane filter (Millipore Millex is suitable), discarding the first 2 mL of filtrate. For solution (2) dilute 5 mL of a 0.1% w/v solution of *bumetanide BPCRS* in *methanol* to 100 mL with the mobile phase.

The chromatographic procedure described under Assay may be used.

Calculate the content of $C_{17}H_{20}N_2O_5S$ in each tablet using the declared content of $C_{17}H_{20}N_2O_5S$ in *bumetanide BPCRS*. The tablets comply with the test if not more than one of the individual values is outside the range 85% to 115% of the average value and none is

www.webofpharma.com

https://thuocngocanh.com/

outside the limits 75% to 125% of the average value. If two or three individual values are outside the limits 85% to 115% of the average value and none is outside the limits 75% to 125%, repeat the determination on a further 20 tablets taken at random. The tablets comply with the test if in the total number of tablets tested not more than three individual values are outside the limits 85% to 115% and none is outside the limits 75% to 125% of the average value.

ASSAY

For bumetanide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a number of whole tablets containing 5 mg of Bumetanide in 5 mL of *methanol* for 3 minutes, add 90 mL of the mobile phase and shake for 30 minutes. Filter to remove the tablet cores, add sufficient of the mobile phase to produce 100 mL, centrifuge for 15 minutes and use the supernatant liquid. If the supernatant liquid is cloudy, filter through a 0.45-µm membrane filter (Millipore Millex is suitable), discarding the first 2 mL of filtrate. For solution (2) dilute 5 mL of a 0.1% w/v solution of *bumetanide BPCRS* in *methanol* to 100 mL with the mobile phase. Solution (3) contains 0.005% w/v of *3-amino-4-phenoxy-5-sulfamoylbenzoic acid BPCRS* in solution (2).

The chromatographic procedure may be carried out using (a) a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher 100 RP-18 is suitable), (b) a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran*, 45 volumes of *water* and 50 volumes of *methanol* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm. Inject separately 20 µL of each solution.

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 15.

Calculate the content of $C_{17}H_{20}N_2O_5S$ in the tablets using the declared content of $C_{17}H_{20}N_2O_5S$ in *bumetanide BPCRS*.

For potassium chloride

Shake 20 whole tablets with 800 mL of *water* for 15 minutes, heating on a water bath if necessary, and allow to stand for 24 hours. Add sufficient *water* to produce 1000 mL, filter and dilute a portion of the filtrate to a suitable concentration. Carry out the method for *atomic emission spectrophotometry*, Appendix II D, measuring at 766.5 nm and using *potassium standard solution (600 ppm K)*, suitably diluted with *water*, to prepare the standard solutions. Each mg of potassium is equivalent to 1.908 mg of KCl.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bumetanide Injection

General Notices

Action and use

Loop diuretic.

DEFINITION

Bumetanide Injection is a sterile solution of Bumetanide in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of bumetanide, $C_{17}H_{20}N_2O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the injection containing 10 mg of Bumetanide with 20 mL of *ether*, filter the ether layer through *anhydrous sodium sulfate* and evaporate to dryness using a rotary evaporator. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of bumetanide *(RS 033)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 7.8, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Adjust the pH of a quantity of the injection containing 5 mg of Bumetanide to 12 using 0.1M *sodium hydroxide* and extract with two 20 mL quantities of *ether*. Discard the ether, adjust the pH to 4 using 1M *acetic acid*, extract with two further 20 mL quantities of *ether*, dry the ether by filtering through *anhydrous sodium sulfate*, wash the filter with 5 mL of *ether* and evaporate the combined filtrate and washings to dryness using a rotary evaporator. Dissolve the residue in 5 mL of *methanol* and centrifuge. Evaporate the supernatant liquid to dryness using a rotary evaporator and dissolve the residue in 0.5 mL of *methanol*.

(2) Dilute 1 volume of solution (1) to 10 volumes with *methanol* and further dilute 1 volume of this solution to 30 volumes with *methanol*.

(3) Dilute 1 volume of solution (2) to 3 volumes with *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

(4) 0.005% w/v of *3-amino-4-phenoxy-5-sulfamoylbenzoic acid BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 25 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

2.5 volumes of *methanol*, 10 volumes of *glacial acetic acid*, 10 volumes of *cyclohexane* and 80 volumes of *chloroform*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* corresponding to 3-amino-4-phenoxy-5-sulfamoylbenzoic acid is not more intense than the spot in the chromatogram obtained with solution (4) (0.5%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.3%);

and not more than two other such spots are more intense than the spot in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection containing 2.5 mg of Bumetanide to 20 mL using a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran* and 45 volumes of *methanol*.

(2) Dilute 10 mL of a 0.025% w/v solution of *bumetanide BPCRS* in a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran* and 45 volumes of *methanol* to 20 mL with *water*.

(3) 0.0125% w/v of *3-amino-4-phenoxy-5-sulfamoylbenzoic acid BPCRS* in solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran*, 45 volumes of *water* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 15.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{20}N_2O_5S$ using the declared content of $C_{17}H_{20}N_2O_5S$ in *bumetanide BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bumetanide Oral Solution

General Notices

Action and use

Loop diuretic.

DEFINITION

Bumetanide Oral Solution is a solution of Bumetanide in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of bumetanide, $C_{17}H_{20}N_2O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (5).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 2.5 volumes of *methanol*, 10 volumes of *glacial acetic acid*, 10 volumes of *cyclohexane* and 80 volumes of *chloroform* as the mobile phase. Apply separately to the plate 25 µL of each of the following solutions. For solution (1) mix a quantity of the oral solution containing 2 mg of Bumetanide with 10 mL of *water* and 0.6 mL of 1M *hydrochloric acid*, add 5 mL of *ethyl acetate*, shake for 15 minutes, centrifuge and decant the ethyl acetate. Add a further 5 mL of *ethyl acetate* to the residue, shake for 15 minutes, centrifuge and decant the ethyl acetate. Evaporate the combined ethyl acetate extracts to dryness using a rotary evaporator and dissolve the residue in 0.5 mL of *methanol*. For solution (2) dilute 1 volume of solution (1) to 10 volumes with *methanol*. For solution (3) dilute 1 volume of solution (2) to 10 volumes with *methanol* and further dilute 1 volume of this solution to 3 volumes with *methanol*. For solution (4) dilute 1 volume of solution (2) to 100 volumes with *methanol*. Solution (5) contains 0.040% w/v of *bumetanide BPCRS* in *methanol*. Solution (6) contains 0.002% w/v of *3-amino-4-phenoxy-5-sulfamoylbenzoic acid BPCRS* in *methanol*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (365 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) corresponding to 3-amino-4-phenoxy-5-sulfamoyl-benzoic acid is not more intense than the spot in the chromatogram obtained with solution (6) (0.5%), any other

www.webofpharma.com

https://thuocngocanh.com/

secondary spot is not more intense than the spot in the chromatogram obtained with solution (3) (0.3%) and not more than two other such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) mix a quantity of the oral solution containing 2.5 mg of Bumetanide with 12.5 mL of *water* and 0.8 mL of 1M *hydrochloric acid*, add 10 mL of *ethyl acetate*, shake for 15 minutes, centrifuge and decant the ethyl acetate. Repeat the extraction procedure twice using a further two 10-mL quantities of *ethyl acetate* and beginning at the words 'add 10 mL of ... '. Evaporate the combined ethyl acetate extracts to dryness using a rotary evaporator, dissolve the residue in 10 mL of a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran* and 45 volumes of *methanol* and dilute to 20 mL with *water*. For solution (2) dilute 5 mL of a 0.025% w/v solution of *bumetanide BPCRS* in a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran* and 45 volumes of *methanol* and dilute to 10 mL with *water*. Inject 20 µL of each solution. Solution (3) contains 0.0125% w/v of *3-amino-4-phenoxy-5-sulfamoyl-benzoic acid BPCRS* in solution (2).

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak ODS is suitable), (b) a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran*, 45 volumes of *water* and 50 volumes of *methanol* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm.

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 15.0.

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{17}H_{20}N_2O_5S$, weight in volume, using the declared content of $C_{17}H_{20}N_2O_5S$ in *bumetanide BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bumetanide Tablets

General Notices

Action and use

Loop diuretic.

DEFINITION

Bumetanide Tablets contain Bumetanide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bumetanide, $C_{17}H_{20}N_2O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Bumetanide with 25 mL of *ether*, filter through *anhydrous sodium sulfate* and evaporate the filtrate to dryness using a rotary evaporator. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of bumetanide *(RS 033)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake mechanically a quantity of the powdered tablets containing 12.5 mg of Bumetanide with 20 mL of a mixture of equal volumes of *acetonitrile* and *methanol* for 20 minutes, centrifuge for 10 minutes, decant and reserve the supernatant liquid. Extract the residue with 5 mL of a mixture of equal volumes of *acetonitrile* and *methanol*, shaking mechanically for 30 seconds, centrifuge for 10 minutes, decant and combine the extracts. Evaporate the combined extracts to dryness under reduced pressure, dissolve the residue in 0.5 mL of *methanol* and centrifuge for 10 minutes.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol* and further dilute 3 volumes of this solution to 10 volumes with *methanol*.

(3) Dilute 1 volume of solution (1) to 10 volumes with *methanol* and further dilute 1 volume of this solution to 100 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a precoated TLC *silica gel F_{254} plate* (Merck silica gel 60 F_{254} plates are suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2.5 volumes of *methanol*, 10 volumes of *glacial acetic acid*, 10 volumes of *cyclohexane* and 80 volumes of *chloroform*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1):

is not more intense than the spot in the chromatogram obtained with solution (2) (0.3%);

and not more than three such spots are more intense than the spot in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Bumetanide comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve one tablet in 10 mL of a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran* and 45 volumes of *methanol*, shake with the aid of ultrasound for 5 minutes, dilute to 20 mL with *water*, filter and use the filtrate.

(2) Dilute 10 mL of a 0.010% w/v solution of *bumetanide BPCRS* in a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran* and 45 volumes of *methanol* to 20 mL with *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Assay may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{20}N_2O_5S$ in each tablet using the declared content of $C_{17}H_{20}N_2O_5S$ in *bumetanide BPCRS*.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the powdered tablets containing 2.5 mg of Bumetanide in 10 mL of a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran* and 45 volumes of *methanol*, shake with the aid of ultrasound for 5 minutes, dilute to 20 mL with *water*, filter and use the filtrate.

(2) Dilute 10 mL of a 0.025% w/v solution of *bumetanide BPCRS* in a mixture of 2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran* and 45 volumes of *methanol* to 20 mL with *water*.

(3) 0.0125% w/v of *3-amino-4-phenoxy-5-sulfamoylbenzoic acid BPCRS* in solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak ODS is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *glacial acetic acid*, 5 volumes of *tetrahydrofuran*, 45 volumes of *water* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 15.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{20}N_2O_5S$ in the tablets using the declared content of $C_{17}H_{20}N_2O_5S$ in *bumetanide BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bupivacaine and Adrenaline Injection / Bupivacaine and Epinephrine Injection

General Notices

Action and use

Local anaesthetic.

DEFINITION

Bupivacaine and Adrenaline Injection is a sterile solution of Bupivacaine Hydrochloride and Adrenaline Acid Tartrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of anhydrous bupivacaine hydrochloride, $C_{18}H_{28}N_2O,HCl$

92.5 to 107.5% of the stated amount.

Content of adrenaline, $C_9H_{13}NO_3$

80.0 to 120.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel precoated plate (Merck silica gel G60 plates are suitable) and a mixture of 5 volumes of *methanol* and 95 volumes of *dichloromethane* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) dilute a quantity of the injection, if necessary, with *water* to produce a solution containing 0.2% w/v of Bupivacaine Hydrochloride. Solution (2) contains 0.2% w/v of *bupivacaine hydrochloride BPCRS* in *water*. Solution (3) contains 0.2% w/v of *bupivacaine hydrochloride BPCRS* and 0.2% w/v of *lidocaine hydrochloride BPCRS* in *water*. After removal of the plate, dry it in a current of cold air, heat at 110° for 1 hour, place the hot plate in a tank of chlorine gas prepared by the addition of *hydrochloric acid* to a 5% w/v solution of *potassium permanganate* contained in a beaker placed in the tank and allow to stand for 2 minutes. Dry the plate in a current of cold air until an area of the plate below the line of application gives at most a very faint blue colour with a 0.5% w/v solution of *potassium iodide* in *starch mucilage*; avoid prolonged exposure to cold air. Spray the plate with a 0.5% w/v solution of *potassium iodide* in *starch mucilage*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots.

www.webofpharma.com

https://thietkuocngocanh.com/

B. In the Assay for adrenaline, the chromatogram obtained with solution (2) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (1).

TESTS

Acidity

pH, 3.0 to 5.5, Appendix V L.

2,6-Dimethylaniline; Related bases

Complies with the requirements stated under Bupivacaine Injection.

ASSAY

For anhydrous bupivacaine hydrochloride

Carry out the Assay described under Bupivacaine Injection.

For adrenaline

Dissolve 8.0 g of *tetramethylammonium hydrogen sulfate*, 2.2 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* in a mixture of 900 mL of *water* and 100 mL of *methanol*, adjust the pH to 3.5 with 1M *sodium hydroxide* and filter through glass micro fibre paper under reduced pressure (solution A). Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute 5 mL of a 0.001% w/v solution of *adrenaline acid tartrate BPCRS* to 10 mL with solution A. For solution (2) dilute the injection, if necessary, to produce a solution containing the equivalent of 0.0005% w/v of adrenaline and dilute 5 mL of the resulting solution to 10 mL with solution A. For solution (3) mix 5 mL of solution (1) with 5 mL of a 0.001% w/v solution of *noradrenaline acid tartrate* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable), (b) as the mobile phase with a flow rate of 2 mL per minute a solution prepared by adding 4.0 g of *tetramethylammonium hydrogen sulfate*, 1.1 g of *sodium heptanesulfonate* and 2 mL of 0.1M *disodium edetate* to a mixture of 950 mL of *water* and 50 mL of *methanol* and adjusting the pH of the mixture to 3.5 with 1M *sodium hydroxide* and (c) a detection wavelength of 205 nm.

The test is not valid unless the *resolution factor* between the two principal peaks in the chromatogram obtained with solution (3) is at least 2.0.

Calculate the content of $C_9H_{13}NO_3$ in the injection using the declared content of $C_9H_{13}NO_3$ in *adrenaline acid tartrate BPCRS*.

STORAGE

Bupivacaine and Adrenaline Injection should be protected from light.

LABELLING

www.webofpharma.com

https://thietkeuocngocanh.com/

The quantities of the active ingredients are stated in terms of the equivalent amounts of anhydrous bupivacaine hydrochloride and adrenaline (epinephrine).

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bupivacaine and Diamorphine Injection

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Spinal anaesthetic; analgesic.

DEFINITION

Bupivacaine and Diamorphine Injection is a sterile solution of Bupivacaine Hydrochloride and Diamorphine Hydrochloride, made isotonic with Sodium Chloride, in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of anhydrous bupivacaine hydrochloride, $C_{18}H_{28}N_2O,HCl$

95.0 to 105.0% of the stated amount.

Content of diamorphine hydrochloride, $C_{21}H_{23}NO_5,HCl,H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention times of the two principal peaks in the chromatogram obtained with solution (1) correspond to those in the chromatogram obtained with solution (4).

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 4.0 to 5.0, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a 0.9% w/v solution of *sodium chloride*.

(1) Dilute a quantity of the injection to produce a solution containing the equivalent of 0.04% w/v of anhydrous bupivacaine hydrochloride.

(2) 1% w/v of *bupivacaine hydrochloride BPCRS*.

www.webofpharma.com

https://thietbiuocngocanh.com/

(3) 0.03% w/v of *diamorphine hydrochloride BPCRS*.

(4) Mix 1 volume of solution (2) and 1 volume of solution (3) and add sufficient of a 0.9% w/v solution of *sodium chloride* to produce 25 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 260 nm.

(f) Inject 10 µL of each solution.

When the chromatograms are recorded under the prescribed conditions, the retention time of diamorphine hydrochloride is about 3.5 minutes and the retention time of bupivacaine hydrochloride is about 5.5 minutes.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of 0.01M *sodium heptanesulfonate*, containing 0.0075M N,N-*dimethyloctylamine*, which has been adjusted to pH 3.0 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{28}N_2O$,HCl and of $C_{21}H_{23}NO_5$,HCl,H_2O in the injection using the declared content of $C_{18}H_{28}N_2O$,HCl in *bupivacaine hydrochloride BPCRS* and the declared content of $C_{21}H_{23}NO_5$,HCl,H_2O in *diamorphine hydrochloride BPCRS*.

STORAGE

Bupivacaine and Diamorphine Injection should be protected from light.

LABELLING

The label states that the injection is intended for epidural administration. The quantity of Bupivacaine Hydrochloride is stated in terms of the equivalent amount of anhydrous bupivacaine hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bupivacaine and Fentanyl Injection

General Notices

Action and use

Spinal anaesthetic; analgesic.

DEFINITION

Bupivacaine and Fentanyl Injection is a sterile solution of Bupivacaine Hydrochloride and Fentanyl Citrate, made isotonic with Sodium Chloride, in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of anhydrous bupivacaine hydrochloride, $C_{18}H_{28}N_2O,HCl$

95.0 to 105.0% of the stated amount.

Content of fentanyl, $C_{22}H_{28}N_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 220 to 350 nm of the solution obtained in the Assay for anhydrous bupivacaine hydrochloride exhibits two maxima, at 263 nm and at 271 nm.

B. In the Assay for fentanyl, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. Yields reaction A characteristic of *chlorides* and reaction B characteristic of *citrates*, Appendix VI.

TESTS

Acidity

pH, 4.0 to 6.5, Appendix V L.

Related substances (anhydrous bupivacaine hydrochloride)

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the injection being examined.

(2) 0.0004% w/v of *fentanyl citrate BPCRS* in a 0.9% w/v solution of *sodium chloride*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (ProntoSIL C18 EPS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 206 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

0.4 volumes of *orthophosphoric acid*, 30 volumes of *acetonitrile R1* and 70 volumes of *water*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.3% by *normalisation*;

the sum of the areas of any such peaks is not greater than 1.0% by *normalisation*.

Disregard any peak corresponding to the principal peak in the chromatogram obtained with solution (2).

ASSAY

For anhydrous bupivacaine hydrochloride

Dilute a quantity of the injection to contain the equivalent of 0.005% w/v of anhydrous bupivacaine hydrochloride with 0.01M *hydrochloric acid*. Measure the *absorbance* of the resulting solution at the maximum at 263 nm, Appendix II B. Calculate the content of $C_{18}H_{28}N_2O$,HCl taking 14 as the value of A(1%, 1 cm) at the maximum at 263 nm.

For fentanyl

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection, if necessary, with sufficient of a 0.9% w/v solution of *sodium chloride* to produce a solution containing the equivalent of 0.0002% w/v of fentanyl.

(2) 0.0003% w/v of *fentanyl citrate BPCRS* in a 0.9% w/v solution of *sodium chloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 206 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuvienthuocngocanh.com/

7 volumes of 0.1M *sodium heptanesulfonate* containing 0.011% w/v of N,N-*dimethyloctylamine,* adjusted to pH 3.0 with *orthophosphoric acid*, 30 volumes of *acetonitrile R1* and 63 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{28}N_2O$ in the injection using the declared content of $C_{22}H_{28}N_2O$ in *fentanyl citrate BPCRS*.

LABELLING

The quantities of the active ingredients are stated in terms of the equivalent amounts of anhydrous bupivacaine hydrochloride and fentanyl.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bupivacaine Heavy Injection

General Notices

Bupivacaine and Dextrose Injection; Bupivacaine and Glucose Injection

Action and use

Local anaesthetic.

DEFINITION

Bupivacaine Heavy Injection is a sterile solution of Bupivacaine Hydrochloride and either Glucose or Glucose Monohydrate in Water for Injections. No preservative is added. The inclusion of glucose in the formulation assists the gravitational flow of the injection when administered.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of bupivacaine hydrochloride, $C_{18}H_{28}N_2O,HCl,H_2O$

95.0 to 105.0% of the stated amount.

Content of glucose monohydrate, $C_6H_{12}O_{6,}H_2O$

72.0 to 88.0 mg per mL.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. To a volume of the injection containing 50 mg of Bupivacaine Hydrochloride add sufficient 2M *sodium hydroxide* to obtain a pH of 11 and extract with 25 mL of *n-heptane*. Dry the heptane extract over *anhydrous sodium sulfate*, filter, evaporate the filtrate to dryness using a rotary evaporator and dry at 60° at a pressure of 2 kPa for 16 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of bupivacaine *(RS 034)*.

B. Dip, for 1 second, a suitable stick with a reactive pad containing glucose-oxidase, peroxidase and a hydrogen-donating substance, such as *tetramethylbenzidine*, in the injection. Observe the colour of the reactive pad; within 60 seconds the colour changes from yellow to green or blue.

C. In the Assay for bupivacaine, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

D. When heated with *cupri-tartaric solution R1*, a copious precipitate of copper(I) oxide is produced.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acidity

pH, 4.0 to 6.0, Appendix V L.

2,6-Dimethylaniline

To 27.6 g of *sodium dihydrogen phosphate monohydrate* add 7 mL of a solution containing 8.9% w/v of *disodium hydrogen orthophosphate dihydrate* and add sufficient water to produce 1000 mL, if necessary adjust the pH to 5.0 using 1M *orthophosphoric acid* or 1M *sodium hydroxide* (buffer solution).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a volume of the injection with mobile phase if necessary to contain 0.5% w/v of Bupivacaine Hydrochloride.
(2) 0.0004% w/v of *2,6-dimethylaniline*.
(3) 0.0002% w/v of *2,6-dimethylaniline* and 0.0002% w/v of *4-chloroaniline*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil Elite is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use ambient column temperature.
(e) Use an electrochemical detector (direct amperometry) with a glassy carbon working electrode, a silver-silver chloride reference electrode, held at + 0.9 V oxidation potential, and a detector sensitivity of 20 nA/V.
(f) Inject volume of 20 µL of each solution.

MOBILE PHASE

A mixture of 4 volumes of *acetonitrile* and 6 volumes of buffer solution containing 0.006% w/v *disodium edetate* and 0.055% w/v *tetrabutylammonium hydrogen sulfate R1*.

When the chromatogram is recorded under the prescribed conditions the retention time of 2,6-dimethylaniline is about 6.5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to 2,6-dimethylaniline and 4-chloroaniline is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2,6-dimethylaniline is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (800 ppm).

5-Hydroxymethylfurfural and light absorbing impurities

www.webofpharma.com

https://thuocngocanh.com/

Dilute a volume of the injection containing 1.0 g of Glucose Monohydrate to 250 mL with *water*. The *absorbance* of the resulting solution at the maximum at 284 nm is not more than 0.25, Appendix II B.

Related substances

To 0.18 g of *sodium dihydrogen phosphate monohydrate* and 2.9 g of *disodium hydrogen orthophosphate dihydrate* add sufficient water to produce 1000 mL, if necessary adjust the pH to 8.0 using 1M *orthophosphoric acid* or 1M *sodium hydroxide* (buffer solution).

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection if necessary to contain 0.5% w/v of Bupivacaine Hydrochloride.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Flow rate of 1.5 mL per minute.
(d) Use ambient column temperature.
(e) Use a detection wavelength 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of 4 volumes of buffer solution and 6 volumes of *acetonitrile*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the total area of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.05%) and any peak corresponding to 2,6-dimethylaniline.

ASSAY

For bupivacaine hydrochloride

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a volume of the injection if necessary to contain 0.05% w/v of Bupivacaine Hydrochloride.
(2) 0.05% w/v of *bupivacaine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{28}N_2O,HCl,H_2O$ in the injection using the declared content of $C_{18}H_{28}N_2O,HCl,H_2O$ in *bupivacaine hydrochloride BPCRS*.

For glucose

To a quantity containing the equivalent of 2 to 5 g of glucose, $C_6H_{12}O_6$, add 0.2 mL of 5M *ammonia* and sufficient *water* to produce 100 mL. Mix well, allow to stand for 30 minutes and measure the *optical rotation* in a 2-dm tube, Appendix V F. The observed rotation in degrees multiplied by 0.9477 represents the weight in g of glucose, $C_6H_{12}O_6$, in the quantity of the injection taken for assay.

LABELLING

The strength is stated in terms of the equivalent amount of bupivacaine hydrochloride and in terms of the equivalent amount of glucose, $C_6H_{12}O_6$ in a suitable dose-volume.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity F (2,6-dimethylaniline) listed under Bupivacaine Hydrochloride and

1. 5-hydroxymethylfurfural (5-(hydroxymethyl)furan-2-carbaldehyde).

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

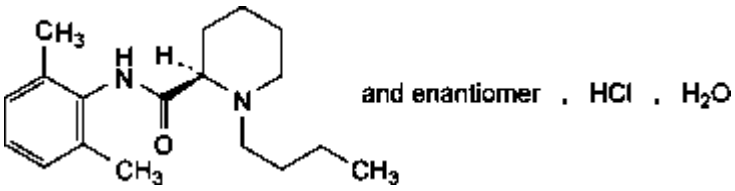
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Bupivacaine Hydrochloride

General Notices

(Ph. Eur. monograph 0541)



$C_{18}H_{29}ClN_2O,H_2O$ 342.9 *73360-54-0*

Action and use

Local anaesthetic.

Preparations

Bupivacaine Injection

Bupivacaine Heavy Injection

Bupivacaine and Adrenaline Injection/Bupivacaine and Epinephrine Injection

Bupivacaine and Diamorphine Injection

Bupivacaine and Fentanyl Injection

Ph Eur

DEFINITION

(2*RS*)-1-Butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide hydrochloride monohydrate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, crystalline powder or colourless crystals.

Solubility

Soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C, D.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *bupivacaine hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 25 mg of *bupivacaine hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *methanol R* (0.1:100 *V/V*).

Application 5 µL.

Development Over a path of 10 cm.

Drying In air.

Detection Spray with *dilute potassium iodobismuthate solution R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of chlorides (2.3.1).

D. Optical rotation (see Tests).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

www.webofpharma.com

https://thuocngocanh.com/

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of *0.01 M sodium hydroxide*; the pH (*2.2.3*) is not less than 4.7. Add 0.4 mL of *0.01 M hydrochloric acid*; the pH is not greater than 4.7.

Optical rotation (*2.2.7*)

-0.10° to + 0.10°.

Dissolve 1.0 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 25 mg of *methyl behenate R* in *methylene chloride R* and dilute to 500 mL with the same solvent.

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of *water R*, add 2.5 mL of *dilute sodium hydroxide solution R* and extract with 2 quantities, each of 5 mL, of the internal standard solution. Filter the lower layer.

Reference solution (a) Dissolve 10 mg of the substance to be examined, 10 mg of *bupivacaine impurity B CRS* and 10 mg of *bupivacaine impurity E CRS* in 2.5 mL of *water R*, add 2.5 mL of *dilute sodium hydroxide solution R* and extract with 2 quantities, each of 5 mL, of the internal standard solution. Filter the lower layer and dilute to 20 mL with the internal standard solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the internal standard solution.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 10.0 mL with the internal standard solution.

Reference solution (d) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the internal standard solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.5 mL/min.

Split ratio 1:12.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
	0	180
Column	0 - 10	180 → 230
	10 - 15	230
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and E.

Relative retention With reference to bupivacaine (retention time = about 10 min): impurity B = about 0.7; impurity E = about 1.1; internal standard = about 1.4.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to bupivacaine and impurity E.

Limits:

— *impurity B*: calculate the ratio (R_1) of the area of the principal peak to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (c); from the chromatogram obtained with the test solution, calculate the ratio of the area of the peak due to impurity B to the area of the peak due to the internal standard: this ratio is not greater than R_1 (0.5 per cent);

— *unspecified impurities*: calculate the ratio (R_2) of the area of the principal peak to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (d); from the chromatogram obtained with the test solution, calculate for each impurity the ratio of the area of any peak, apart from the principal peak, the peak due to impurity B and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than R_2 (0.10 per cent);

— *total*: calculate the ratio (R_3) of the area of the principal peak to the area of the peak due to the internal standard from the chromatogram obtained with reference solution (b); from the chromatogram obtained with the test solution, calculate the ratio of the sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than R_3 (1.0 per cent);

— *disregard limit*: ratio less than 0.05 times R_3 (0.05 per cent).

Impurity F

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 50 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 5.0 mg of *bupivacaine impurity F CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 20 mg of *methyl benzoate R* and 25 mg of *bupivacaine impurity F CRS* in mobile phase A and dilute to 50 mL with mobile phase A. Dilute 3 mL of the solution to 50 mL with mobile phase A. Dilute 1 mL of this solution to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 0.23 g of *sodium dihydrogen phosphate monohydrate R* and 3.626 g of *disodium hydrogen phosphate dihydrate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; mix equal volumes of this solution (pH 8.0) and *acetonitrile for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 15	100 → 80	0 → 20
15 - 25	80	20

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity F.

Relative retention With reference to bupivacaine (retention time = about 20 min): impurity F = about 0.3; methyl benzoate = about 0.4.

System suitability:

— *resolution*: minimum 4.0 between the peaks due to impurity F and methyl benzoate in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 40 for the principal peak in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Limit:

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (10 ppm).

Loss on drying (2.2.32)

4.5 per cent to 6.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 20 mL of *water R* and 25 mL of *ethanol (96 per cent) R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M ethanolic sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 32.49 mg of $C_{18}H_{29}ClN_2O$.

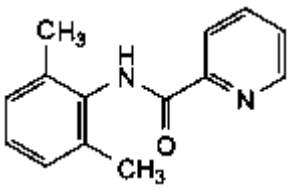
STORAGE

Protected from light.

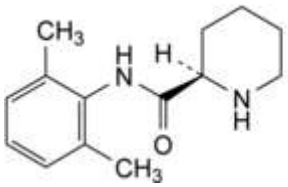
IMPURITIES

Specified impurities *B, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E.*



A. *N*-(2,6-dimethylphenyl)pyridine-2-carboxamide,

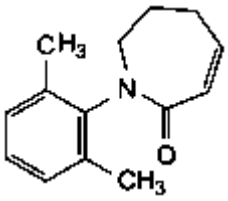


and enantiomer

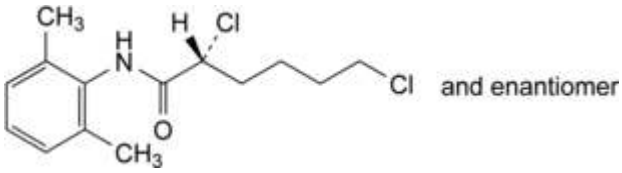
B. (2*RS*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide,

www.webofpharma.com

https://thuocngocanh.com/

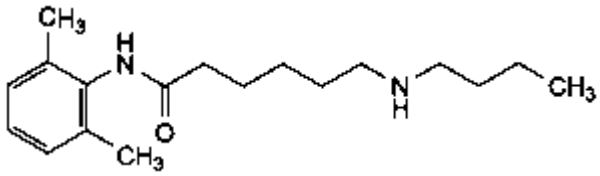


C. 1-(2,6-dimethylphenyl)-1,5,6,7-tetrahydro-2*H*-azepin-2-one,

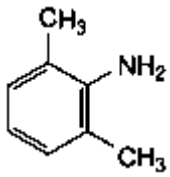


and enantiomer

D. (2*RS*)-2,6-dichloro-*N*-(2,6-dimethylphenyl)hexanamide,



E. 6-(butylamino)-*N*-(2,6-dimethylphenyl)hexanamide,



F. 2,6-dimethylaniline.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bupivacaine Injection

General Notices

Action and use

Local anaesthetic.

DEFINITION

Bupivacaine Injection is a sterile solution of Bupivacaine Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of anhydrous bupivacaine hydrochloride, $C_{18}H_{28}N_2O,HCl$

92.5 to 107.5% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. To a volume of the injection containing the equivalent of 25 mg of anhydrous bupivacaine hydrochloride add 2 mL of 13.5M *ammonia*, shake and filter. Wash the precipitate with *water* and dry at 60° at a pressure of 2 kPa for 16 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of bupivacaine *(RS 034)*.

B. To a volume of the injection containing the equivalent of 50 mg of anhydrous bupivacaine hydrochloride add 2 mL of a 10% w/v solution of *disodium hydrogen orthophosphate* and sufficient *iodinated potassium iodide solution* to produce a distinct brown colour. Remove the excess iodine by adding 0.1M *sodium thiosulfate*. No pink colour is produced.

TESTS

Acidity

pH, 4.0 to 6.5, Appendix V L.

2,6-Dimethylaniline

To a volume of the injection containing the equivalent of 25 mg of anhydrous bupivacaine hydrochloride add sufficient *water*, if necessary, to produce 10 mL, add 2M *sodium hydroxide* until the solution is just alkaline and extract with three 5 mL quantities of *dichloromethane*. Dry the combined dichloromethane extracts over *anhydrous sodium sulfate*, filter, wash with a further 5 mL of *dishloromethane* and evaporate the filtrate to dryness using a rotary evaporator. Dissolve the residue in 2 mL of *methanol*, add 1 mL of a 1% w/v solution of *4-*

www.webofpharma.com

https://thietbiuocngocanh.com/

dimethylaminobenzaldehyde in *methanol* and 2 mL of *glacial acetic acid* and allow to stand at room temperature for 10 minutes. The yellow colour produced is not more intense than the colour produced by repeating the operation using 10 mL of a solution in *water* containing 1 µg of *2,6-dimethylaniline* per mL in place of the injection (400 ppm).

Bupivacaine-related bases

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 0.1 volume of 13.5M *ammonia* and 100 volumes of *methanol* as the mobile phase but allowing the solvent front to ascend 10 cm above the line of application. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) evaporate a volume of the injection containing the equivalent of 0.1 g of anhydrous bupivacaine hydrochloride using a rotary evaporator, add sufficient *methanol* to the residue to produce 2 mL, mix, centrifuge and use the supernatant liquid. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *methanol*. After removal of the plate, allow it to dry in air and spray with *dilute potassium iodobismuthate solution*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute a quantity of the injection with sufficient of the mobile phase to produce a solution containing 0.0025% w/v of anhydrous bupivacaine hydrochloride. Solution (2) contains 0.0025% w/v of *bupivacaine hydrochloride BPCRS* in the mobile phase. For solution (3) prepare a 0.1% w/v solution of *2,6-dimethylaniline* in *acetonitrile*, dilute 10 volumes to 20 volumes with the mobile phase and then dilute 1 volume of the resulting solution to 100 volumes with solution (2).

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable), (b) a mixture of 40 volumes of 0.02M *phosphate buffer pH 8.0* and 60 volumes of *acetonitrile* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 240 nm. Inject 20 µL of each solution.

The test is not valid unless in the chromatogram obtained with solution (3) the *resolution factor* between the two principal peaks is at least 8.

Calculate the content of $C_{18}H_{28}N_2O$,HCl in the injection using the declared content of $C_{18}H_{28}N_2O$,HCl in *bupivacaine hydrochloride BPCRS*.

LABELLING

The strength is stated in terms of the equivalent amount of anhydrous bupivacaine hydrochloride in a suitable dose-volume.

© Crown Copyright 2022

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

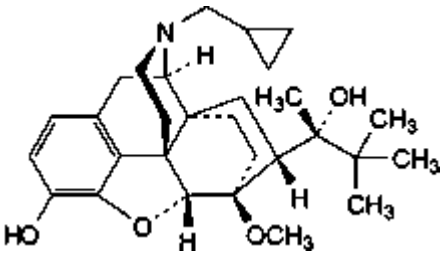
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buprenorphine

General Notices

(Ph. Eur. monograph 1180)



$C_{29}H_{41}NO_4$ 467.6 *52485-79-7*

Action and use

Opioid receptor partial agonist; analgesic.

Preparation

Buprenorphine Transdermal Patches

Ph Eur

DEFINITION

(2*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in acetone, soluble in methanol, slightly soluble in cyclohexane. It dissolves in dilute solutions of acids.

mp

www.webofpharma.com

https://thuocngocanh.com/

About 217 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *buprenorphine CRS*.

TESTS

Solution S

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

-103 to -107 (dried substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *buprenorphine for system suitability CRS* (containing impurities A, B, F, G, H and J) in 1.0 mL of *methanol R*.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 10 volumes of *acetonitrile R* and 90 volumes of the following solution: dissolve 5.44 g of *potassium dihydrogen phosphate R* in 900 mL of *water R*, adjust to pH 4.5 with a 5 per cent *V/V* solution of *phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *acetonitrile R*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	89	11
2 - 12	89 → 64	11 → 36
12 - 15	64 → 41	36 → 59
15 - 20	41 → 39	59 → 61

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with *buprenorphine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, F, G, H and J.

Relative retention With reference to buprenorphine (retention time = about 8.5 min): impurity B = about 0.4; impurity J = about 1.1; impurity F = about 1.27; impurity H = about 1.33; impurity A = about 1.40; impurity G = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to buprenorphine and impurity J.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 0.3;

— *impurity H*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *impurities A, B, F, J*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.400 g in 40 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 46.76 mg of $C_{29}H_{41}NO_4$.

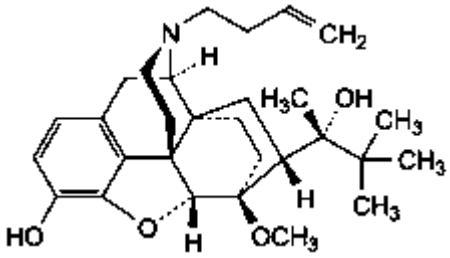
STORAGE

Protected from light.

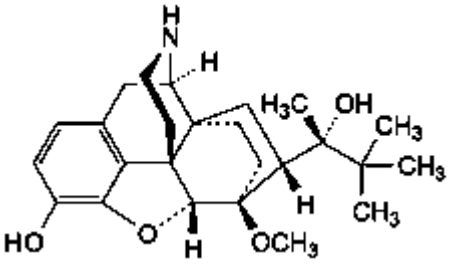
IMPURITIES

Specified impurities *A, B, F, G, H, J.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, I.*



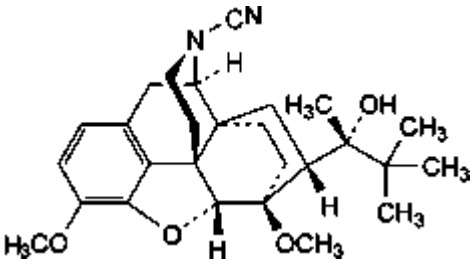
A. (2*S*)-2-[17-(but-3-enyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol,



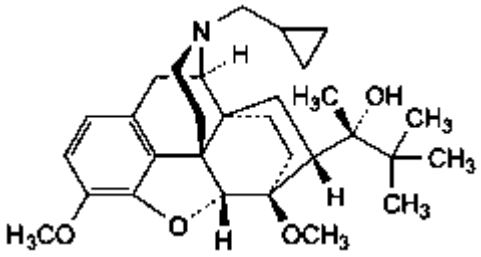
B. (2*S*)-2-(4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl)-3,3-dimethylbutan-2-ol (norbuprenorphine),

www.webofpharma.com

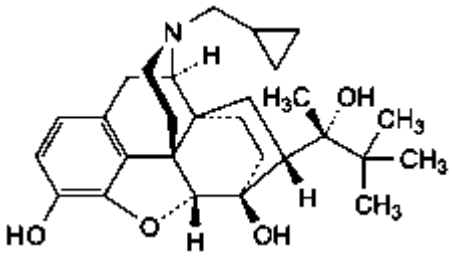
https://thuocngocanh.com/



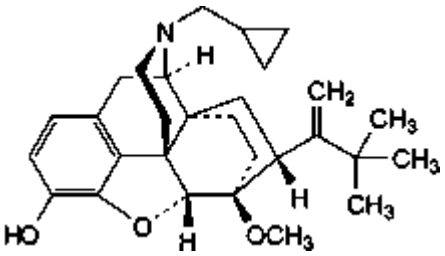
C. 4,5α-epoxy-7α-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-3,6-dimethoxy-6α,14-ethano-14α-morphinan-17-carbonitrile,



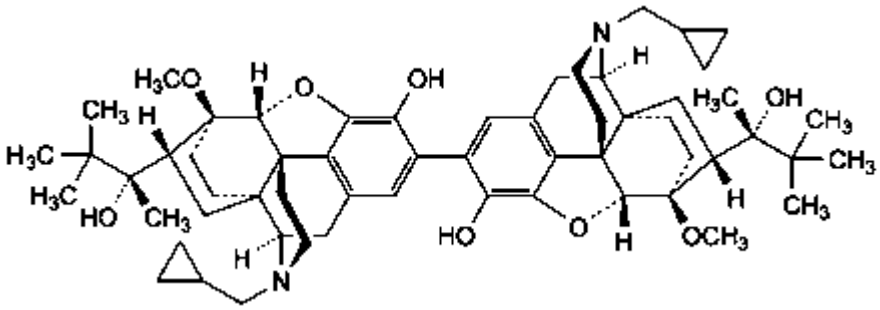
D. (2*S*)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dimethoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol (3-*O*-methylbuprenorphine),



E. (2*S*)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dihydroxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol (6-*O*-desmethylbuprenorphine),



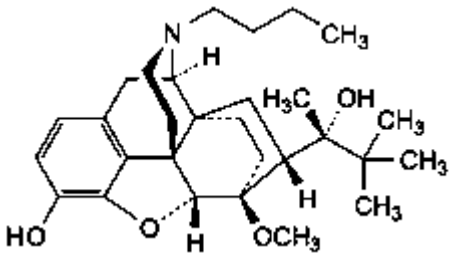
F. 17-(cyclopropylmethyl)-4,5α-epoxy-6-methoxy-7α-[1-(1,1-dimethylethyl)ethenyl]-6α,14-ethano-14α-morphinan-3-ol,



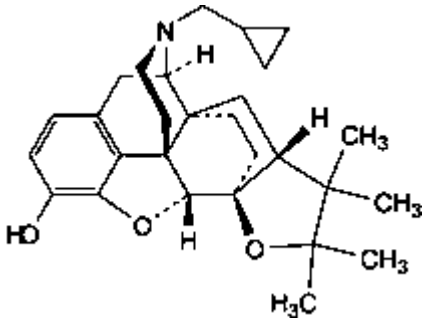
www.webofpharma.com

https://thuocngocanh.com/

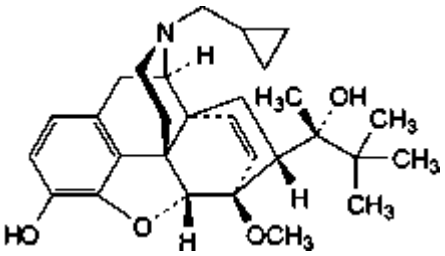
G. 17,17′-di(cyclopropylmethyl)-4,5α;4′,5α′-diepoxy-7α,7α′-di[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6,6′-dimethoxy-2,2′-bi(6α,14-ethano-14α-morphinan)-3,3′-diol (2,2′-bibuprenorphine),



H. (2*S*)-2-[17-butyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]3,3-dimethylbutan-2-ol,



I. 17-(cyclopropylmethyl)-4″,4″,5″,5″-tetramethyl-4″,5″dihydro-(7β*H*)-6α,14-ethano-(5β*H*)-difurano[2′,3′,4′,5′:4,12,13,5;2″,3″:6,7]-14α-morphinan-3-ol,



J. (2*S*)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-etheno-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

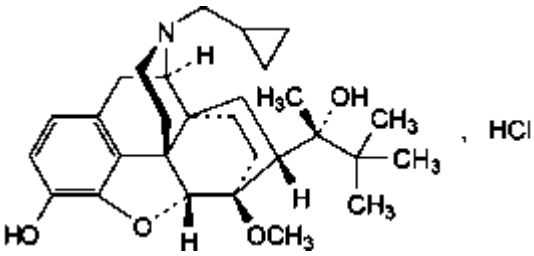
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buprenorphine Hydrochloride

General Notices

(Ph. Eur. monograph 1181)



$C_{29}H_{42}ClNO_4$ 504.1 *53152-21-9*

Action and use

Opioid receptor partial agonist; analgesic.

Preparations

Buprenorphine Injection

Buprenorphine Sublingual Tablets

Ph Eur

DEFINITION

(2*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison buprenorphine hydrochloride CRS.

B. 3 mL of solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.250 g in 5.0 mL of methanol R and, while stirring, dilute to 25.0 mL with carbon dioxide-free water R.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 10.0 mL of solution S add 0.05 mL of methyl red solution R. Not more than 0.2 mL of 0.02 M sodium hydroxide or 0.02 M hydrochloric acid is required to change the colour of the indicator.

Specific optical rotation (2.2.7)

-92 to -98 (dried substance).

Dissolve 0.200 g in methanol R and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in methanol R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with methanol R. Dilute 1.0 mL of this solution to 10.0 mL with methanol R.

Reference solution (b) Dissolve 5 mg of buprenorphine for system suitability CRS (containing impurities A, B, F, G, H and J) in 1.0 mL of methanol R.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 30 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: mix 10 volumes of *acetonitrile R* and 90 volumes of the following solution: dissolve 5.44 g of *potassium dihydrogen phosphate R* in 900 mL of *water R*, adjust to pH 4.5 with a 5 per cent *V/V* solution of *phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	89	11
2 - 12	89 → 64	11 → 36
12 - 15	64 → 41	36 → 59
15 - 20	41 → 39	59 → 61

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with *buprenorphine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, F, G, H and J.

Relative retention With reference to buprenorphine (retention time = about 8.5 min): impurity B = about 0.4; impurity J = about 1.1; impurity F = about 1.27; impurity H = about 1.33; impurity A = about 1.40; impurity G = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to buprenorphine and impurity J.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 0.3;

— *impurity H*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *impurities A, B, F, J*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity G*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by heating in an oven at 115-120 °C.

ASSAY

Dissolve 0.400 g in a mixture of 5 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 50.41 mg of $C_{29}H_{42}ClNO_4$.

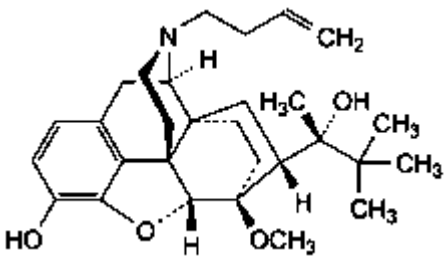
STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B, F, G, H, J.

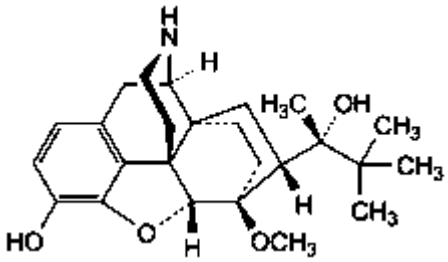
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E, I.



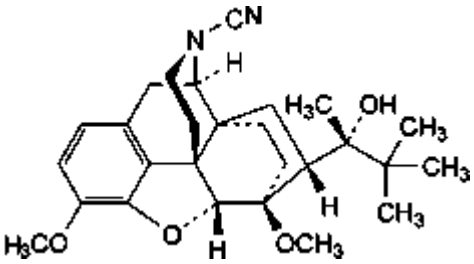
A. (2*S*)-2-[17-(but-3-enyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol,

www.webofpharma.com

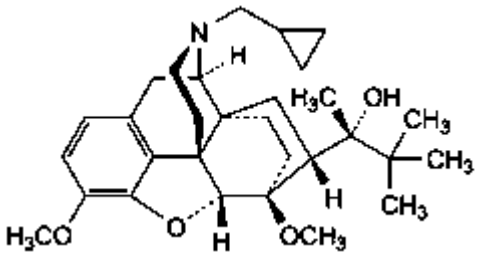
https://thuocngocanh.com/



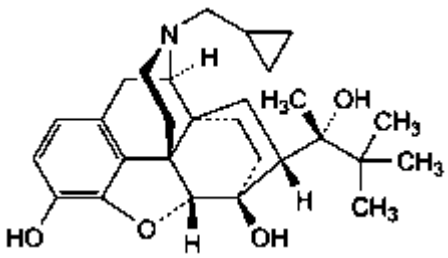
B. (2*S*)-2-(4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl)-3,3-dimethylbutan-2-ol (norbuprenorphine),



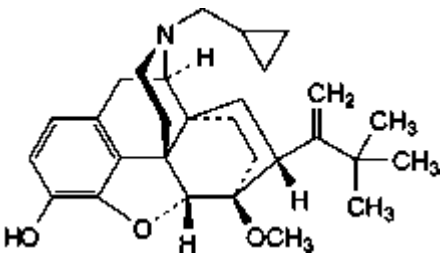
C. 4,5α-epoxy-7α-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-3,6-dimethoxy-6α,14-ethano-14α-morphinan-17-carbonitrile,



D. (2*S*)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dimethoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol (3-*O*-methylbuprenorphine),



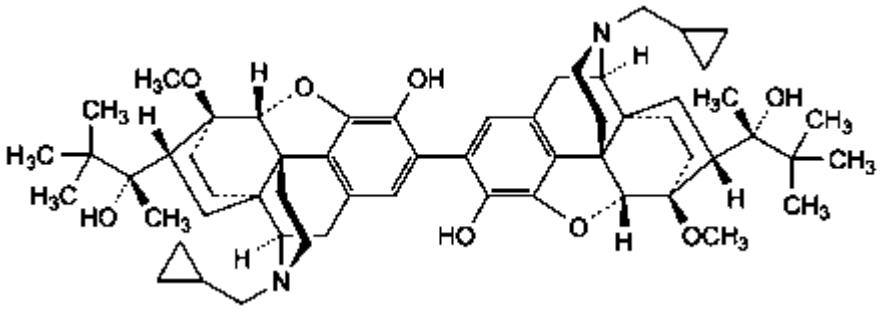
E. (2*S*)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dihydroxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol (6-*O*-desmethylbuprenorphine),



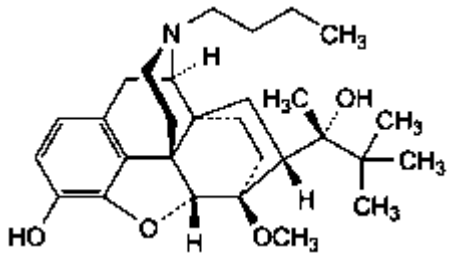
F. 17-(cyclopropylmethyl)-4,5α-epoxy-6-methoxy-7α-[1-(1,1-dimethylethyl)ethenyl]-6α,14-ethano-14α-morphinan-3-ol,

www.webofpharma.com

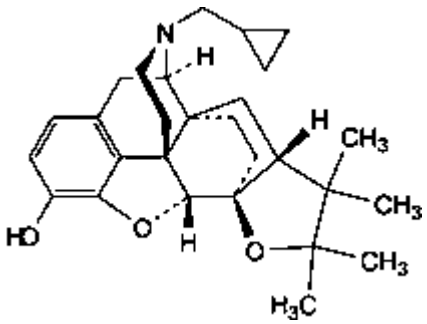
https://thuocngocanh.com/



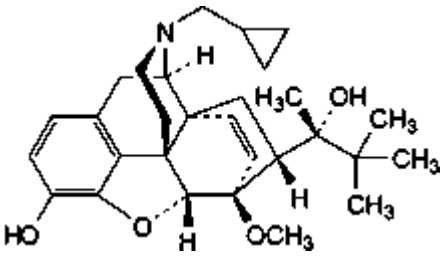
G. 17,17′-di(cyclopropylmethyl)-4,5α;4′,5α′-diepoxy-7α,7α′-di[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6,6′-dimethoxy-2,2′-bi(6α,14-ethano-14α-morphinan)-3,3′-diol (2,2′-bibuprenorphine),



H. (2*S*)-2-[17-butyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]3,3-dimethylbutan-2-ol,



I. 17-(cyclopropylmethyl)-4″,4″,5″,5″-tetramethyl-4″,5″dihydro-(7β*H*)-6α,14-ethano-(5β*H*)-difurano[2′,3′,4′,5′:4,12,13,5;2″,3″:6,7]-14α-morphinan-3-ol,



J. (2*S*)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-etheno-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buprenorphine Injection

General Notices

Action and use

Opioid receptor partial agonist; analgesic.

DEFINITION

Buprenorphine Injection is a sterile solution containing Buprenorphine Hydrochloride.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of buprenorphine, $C_{29}H_{41}NO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the injection containing the equivalent of 0.3 mg of buprenorphine add 5 mL of *water*, add sufficient *dilute hydrochloric acid* to turn litmus paper red and add 1 mL of *potassium iodobismuthate solution*. An orange-red precipitate is formed.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH 3.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection, if necessary, with sufficient *methanol* to produce a solution containing the equivalent of 0.03% w/v of buprenorphine and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*, further dilute 1 volume of this solution to 2 volumes with *methanol*.

(3) 0.05% w/v of *buprenorphine for system suitability EPCRS* in *methanol*.

(4) Dilute 1 volume of solution (2) to 5 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (50 mm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters SunFire C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of *acetonitrile* and 90 volumes of a 0.544% w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 4.5 with *dilute orthophosphoric acid*.

Mobile phase B *acetonitrile*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	89	11	isocratic
2-12	89→64	11→36	linear gradient
12-15	64→41	36→59	isocratic
15-20	41→39	59→61	linear gradient
20-21	39→89	61→11	linear gradient
21-30	89	11	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to buprenorphine and buprenorphine impurity J is at least 3.0.

LIMITS

Identify any peak corresponding to impurity G using solution (3) and multiply the area of this peak by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any other *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thietbiuocngocanh.com/

(1) Dilute a quantity of the injection, if necessary, with sufficient *methanol* to produce a solution containing the equivalent of 0.01% w/v of buprenorphine and filter.

(2) 0.01% w/v of *buprenorphine hydrochloride BPCRS* in *methanol*.

(3) 0.05% w/v of *buprenorphine for system suitability EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used. Inject 10 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to buprenorphine and buprenorphine impurity J is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{41}NO_4$ in the injection using the declared content of $C_{29}H_{41}NO_4$,HCl in *buprenorphine hydrochloride BPCRS*. Each mg of $C_{29}H_{41}NO_4$,HCl is equivalent to 0.9276 mg of $C_{29}H_{41}NO_4$.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of buprenorphine.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buprenorphine Sublingual Tablets

General Notices

Action and use

Opioid receptor partial agonist; analgesic.

DEFINITION

Buprenorphine Sublingual Tablets contain Buprenorphine Hydrochloride. They may be flavoured.

The tablets comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of buprenorphine, $C_{29}H_{41}NO_4$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Evaporate 10 mL of solution (1) obtained in the Assay to dryness. Dissolve the residue in 5 mL of *water*, add sufficient *dilute hydrochloric acid* to turn litmus paper red and add 1 mL of *potassium iodobismuthate solution*. An orange-red precipitate is formed.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing the equivalent of 4 mg of buprenorphine with 4 mL of *methanol* and filter.

(2) Dilute 2 volumes of solution (1) to 100 volumes with *methanol*.

(3) 0.1% w/v of *buprenorphine for system suitability EPCRS* in *methanol*.

(4) Dilute 1 volume of solution (2) to 20 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (50 mm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Sunfire C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 30°.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 240 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of *acetonitrile* and 90 volumes of a 0.544% w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 4.5 with *dilute orthophosphoric acid*.

Mobile phase B *acetonitrile*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	89	11	isocratic
2-12	89→64	11→36	linear gradient
12-15	64→41	36→59	isocratic
15-20	41→39	59→61	linear gradient
20-21	39→89	61→11	linear gradient
21-30	89	11	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to buprenorphine and buprenorphine impurity J is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

Identify any peak corresponding to impurity G using solution (3) and multiply the area of this peak by a correction factor of 0.3.

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of not more than one *secondary peak* is greater than half the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks* is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (6%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or 2% w/v of Buprenorphine Hydrochloride comply with the requirements stated under Tablets using the following method of analysis.

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To one tablet add 1 mL of *methanol*, mix with the aid of ultrasound and add sufficient mobile phase to produce a solution containing the equivalent of 0.004% w/v of buprenorphine.

(2) 0.004% w/v of *buprenorphine hydrochloride BPCRS* in *methanol*.

(3) 0.1% w/v of *buprenorphine for system suitability EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used. Inject 25 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to buprenorphine and buprenorphine impurity J is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{41}NO_4$ in each tablet using the declared content of $C_{29}H_{41}NO_4$,HCl in *buprenorphine hydrochloride BPCRS*. Each mg of $C_{29}H_{41}NO_4$,HCl is equivalent to 0.9276 mg of $C_{29}H_{41}NO_4$.

ASSAY

For tablets containing less than 2 mg and/or 2% w/v of Buprenorphine Hydrochloride

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more, or 2% w/v or more of Buprenorphine Hydrochloride

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 2 mg of buprenorphine with 10 mL of *methanol*, add sufficient *methanol* to produce 20 mL and filter.

(2) 0.01% w/v of *buprenorphine hydrochloride BPCRS* in *methanol*.

(3) 0.1% w/v of *buprenorphine for system suitability EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to buprenorphine and buprenorphine impurity J is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{41}NO_4$ in the tablets using the declared content of $C_{29}H_{41}NO_4$,HCl in *buprenorphine hydrochloride BPCRS*. Each mg of $C_{29}H_{41}NO_4$,HCl is equivalent to 0.9276 mg of $C_{29}H_{41}NO_4$.

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of buprenorphine.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buprenorphine Transdermal Patches

General Notices

Action and use

Opioid receptor partial agonist; analgesic.

DEFINITION

Buprenorphine Transdermal Patches contain Buprenorphine in a suitable matrix or reservoir presentation.

PRODUCTION

A suitable test is carried out to demonstrate the appropriate release of buprenorphine.

The transdermal patches comply with the requirements stated under Transdermal Patches and with the following requirements.

Content of buprenorphine, $C_{29}H_{41}NO_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Evaporate 10 mL of solution (1) obtained in the Assay to dryness. Dissolve the residue in 5 mL of *water*, add sufficient *dilute hydrochloric acid* to turn litmus paper red and add 1 mL of *potassium iodobismuthate solution*. An orange-red precipitate is formed.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Remove the release liners from the patches. Mix, with the aid of ultrasound, a quantity of whole patches with sufficient *methanol* to produce a solution containing 0.1% w/v of Buprenorphine.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) 0.1% w/v of *buprenorphine for system suitability EPCRS* in *methanol*.

(4) Dilute 1 volume of solution (2) to 10 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (50 mm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Sunfire C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of *acetonitrile* and 90 volumes of a 0.544% w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 4.5 with *dilute orthophosphoric acid*.

Mobile phase B *acetonitrile*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	89	11	isocratic
2-12	89→64	11→36	linear gradient
12-15	64→41	36→59	isocratic
15-20	41→39	59→61	linear gradient
20-21	39→89	61→11	linear gradient
21-30	89	11	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to buprenorphine (retention time about 9 minutes) are impurity B, about 0.4; buprenorphine *N*-oxide, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to buprenorphine and buprenorphine impurity J is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity G using solution (3) and multiply the area of this peak by a correction factor of 0.3;

the area of any peak due to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any peak due to buprenorphine *N*-oxide is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

www.webofpharma.com

https://thietbiuocngocanh.com/

the area of any *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any other *secondary peaks* is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Comply with the requirements stated under *uniformity of content*, Appendix XII C3, Test C, with respect to the individual content of each dosage unit and using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Remove the release liner from the patch. Place the patch in a flask containing sufficient *methanol* to produce a solution containing 0.1% w/v of Buprenorphine, mix with the aid of ultrasound and filter.
(2) 0.01% w/v of *buprenorphine hydrochloride BPCRS* in methanol.
(3) 0.1% w/v of *buprenorphine for system suitability EPCRS* in methanol.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to buprenorphine and buprenorphine impurity J is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{29}H_{41}NO_4$ in the transdermal patch using the declared content of $C_{29}H_{41}NO_4$,HCl in *buprenorphine hydrochloride BPCRS*. Each mg of $C_{29}H_{41}NO_4$,HCl is equivalent to 0.9276 mg of $C_{29}H_{41}NO_4$.

ASSAY

Use the average of the 10 results obtained in the test for Uniformity of content.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

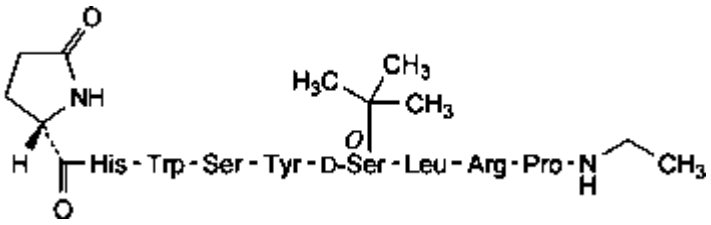
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buserelin

General Notices

(Ph. Eur. monograph 1077)



$C_{60}H_{86}N_{16}O_{13}$ 1239 *57982-77-1*

Action and use

Gonadotrophin releasing hormone (gonadorelin) analogue; treatment of prostate cancer.

Ph Eur

DEFINITION

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-(1,1-dimethylethyl)-D-seryl-L-leucyl-L-arginyl-*N*-ethyl-L-prolinamide.

Synthetic nonapeptide analogue of human gonadotrophin-releasing hormone GnRH with agonistic activity to gonadorelin. It is obtained by chemical synthesis and is available as an acetate.

Content

95.0 per cent to 102.0 per cent (anhydrous, acetic acid-free substance).

CHARACTERS

Appearance

White or slightly yellowish powder, hygroscopic.

Solubility

Sparingly soluble in water and in dilute acids.

IDENTIFICATION

Carry out either tests A and B or tests A and C.

www.webofpharma.com

https://thuocngocanh.com/

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

B. Nuclear magnetic resonance spectrometry (*2.2.64*).

Preparation 4 mg/mL solution in a mixture of 20 volumes of *deuterated acetic acid R* and 80 volumes of *deuterium oxide R*.

Comparison Dissolve the contents of a vial of *buserelin for NMR identification CRS* in a mixture of 20 volumes of *deuterated acetic acid R* and 80 volumes of *deuterium oxide R* to obtain a concentration of 4 mg/mL.

Operating conditions:

— *field strength*: minimum 300 MHz;

— *temperature*: 27 °C.

Results Examine the ^{1}H NMR spectrum from 0 to 9 ppm. The ^{1}H NMR spectrum obtained is qualitatively similar to the ^{1}H NMR spectrum obtained with *buserelin for NMR identification CRS*.

C. Amino acid analysis (*2.2.56*). Method 1 for hydrolysis and method 1 for analysis are suitable.
Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids, taking 1/6 of the sum of the number of moles of glutamic acid, histidine, tyrosine, leucine, arginine and proline as equal to 1. The values fall within the following limits: serine 1.4 to 2.0; proline 0.8 to 1.2; glutamic acid 0.9 to 1.1; leucine 0.9 to 1.1; tyrosine 0.9 to 1.1; histidine 0.9 to 1.1; arginine 0.9 to 1.1. Not more than traces of other amino acids are present.

TESTS

Appearance of solution

A 10 g/L solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

-58 to -49 (anhydrous, acetic acid-free substance), determined on a 10 g/L solution.

Specific absorbance (*2.2.25*)

49 to 56, measured at the absorption maximum at 278 nm (anhydrous, acetic acid-free substance).

Dissolve 10.0 mg in 100.0 mL of *0.01 M hydrochloric acid*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 5.0 mg of the substance to be examined in 5.0 mL of the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve the contents of a vial of *D-His-buserelin CRS* (impurity A) in the mobile phase. Dilute an appropriate volume of this solution in the mobile phase to obtain a final concentration of 1 mg/mL. Add 1.0 mL of the test solution to 1.0 mL of this solution.

Reference solution (b) Dissolve the contents of a vial of *buserelin CRS* in the mobile phase. Dilute an appropriate volume of this solution in the mobile phase to obtain a final concentration of 1.0 mg/mL.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve the contents of a vial of *buserelin for peak identification CRS* (containing impurities F and G) in the mobile phase. Dilute an appropriate volume of this solution in the mobile phase to obtain a final concentration of 1 mg/mL.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 42 °C.

Mobile phase Mix 200 mL of *acetonitrile R* and 700 mL of an 11.2 g/L solution of *phosphoric acid R* previously adjusted to pH 2.5 with *triethylamine R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (a), (c) and (d).

Run time 60 min.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities F and G.

Relative retention With reference to buserelin (retention time = about 23 min): impurity F = about 0.83; impurity A = about 0.91; impurity G = about 1.26.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurity A and buserelin.

Calculation of percentage contents:

— for each impurity, use the concentration of buserelin in reference solution (c).

Limits:

— *impurity A*: maximum 2.5 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *impurity F*: maximum 1.0 per cent;

— *impurity G*: maximum 1.0 per cent;

— *unspecified impurities*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 4.0 per cent;

— *reporting threshold*: 0.1 per cent.

Acetic acid (2.5.34)

3.0 per cent to 7.0 per cent.

Test solution Dissolve 20.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of solvents.

Water (2.5.12)

Maximum 4.0 per cent, determined on 80.0 mg.

Bacterial endotoxins (2.6.14)

Less than 55.5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (b).

Calculate the percentage content of buserelin ($C_{60}H_{86}N_{16}O_{13}$) taking into account the assigned content of $C_{60}H_{86}N_{16}O_{13}$ in *buserelin CRS*.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states:

— the mass of peptide in the container;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

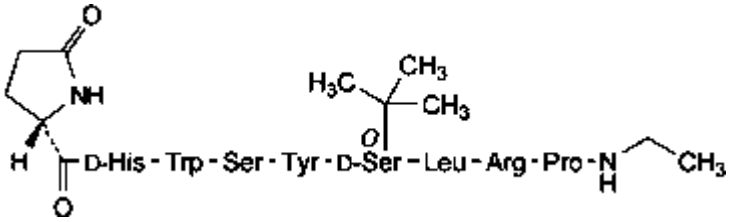
IMPURITIES

www.webofpharma.com

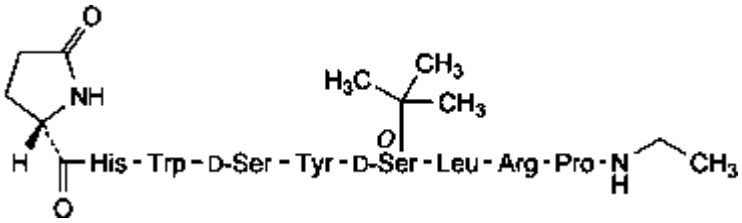
https://thuvienthuocngocanh.com/

Specified impurities A, F, G.

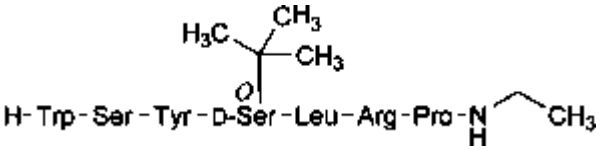
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E.



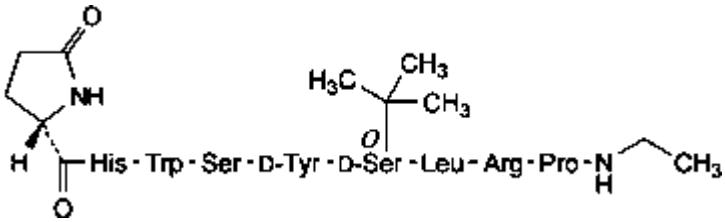
A. [2-D-histidine]buserelin,



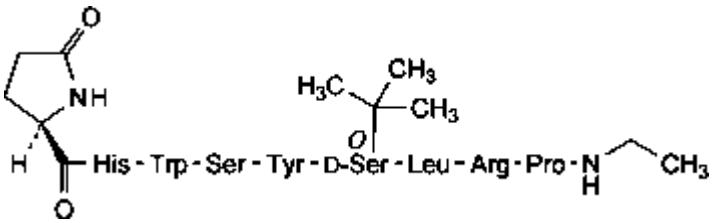
B. [4-D-serine]buserelin,



C. buserelin-(3-9)-peptide,



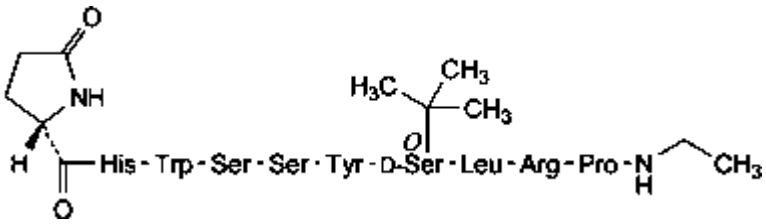
D. [5-D-tyrosine]buserelin,



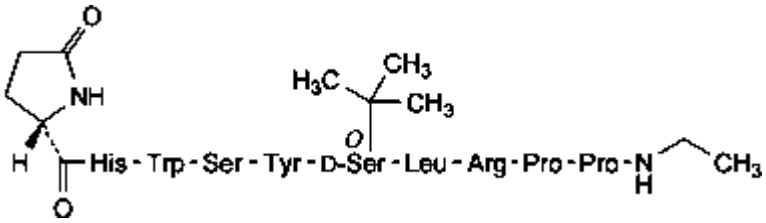
E. [1-(5-oxo-D-proline)]buserelin,

www.webofpharma.com

https://thuocngocanh.com/



F. endo-3a-serine-buserelin,



G. endo-8a-proline-buserelin.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

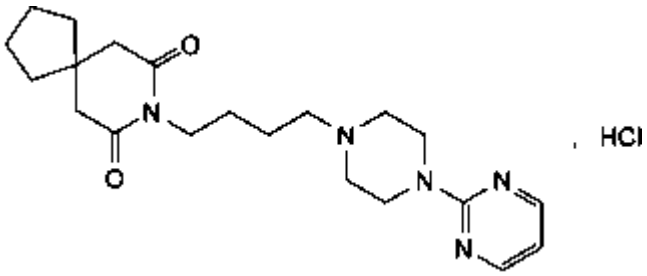
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Buspirone Hydrochloride

General Notices

(Ph. Eur. monograph 1711)



$C_{21}H_{32}ClN_5O_2$ 422.0 *33386-08-2*

Action and use

Non-benzodiazepine hypnotic; treatment of anxiety.

Ph Eur

DEFINITION

8-[4-[4-(Pyrimidin-2-yl)piperazin-1-yl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in acetone.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *buspirone hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 25.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve the contents of a vial of *buspirone for system suitability CRS* (containing impurities E, G, J, L and N) in 2.0 mL of mobile phase A and sonicate for 10 min.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 950 volumes of a solution containing 6.8 g/L of *potassium dihydrogen phosphate R* and 0.93 g/L of *sodium hexanesulfonate monohydrate R*, previously adjusted to pH 3.4 with *phosphoric acid R* and 50 volumes of *acetonitrile R1*;

— *mobile phase B*: mix 250 volumes of a solution containing 3.4 g/L of *potassium dihydrogen phosphate R* and 3.52 g/L of *sodium hexanesulfonate monohydrate R*, previously adjusted to pH 2.2 with *phosphoric acid R* and 750 volumes of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	90	10
6 - 34	90 → 42	10 → 58
34 - 45	42	58
45 - 55	42 → 0	58 → 100
55 - 56	0 → 100	100 → 0

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
56 - 60	100	0
60 - 61	100 → 90	0 → 10

Flow rate 1 mL/min.

Detection Variable wavelength spectrophotometer capable of operating at 240 nm and at 210 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *buspirone for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities E, G, J, L and N.

Relative retention at 240 nm With reference to buspirone (retention time = about 25 min): impurity A = about 0.2; impurity B = about 0.3; impurity C = about 0.6; impurity D = about 0.7; impurity E = about 0.8; impurity F = about 0.9; impurity G = about 1.05; impurity H = about 1.1; impurity I = about 1.2; impurity J = about 1.5.

Relative retention at 210 nm With reference to buspirone (retention time = about 25 min): impurity K = about 0.6; impurity L = about 1.7; impurity M = about 1.8; impurity N = about 1.9.

System suitability Reference solution (b):

— *peak-to-valley ratio at 240 nm*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to buspirone;

— *resolution at 210 nm*: minimum 4.0 between the peaks due to impurity L and impurity N;

— the chromatograms obtained are similar to the chromatograms supplied with *buspirone for system suitability CRS*.

Limits Spectrophotometer at 240 nm:

— *correction factor*: for the calculation of content, multiply the peak area of impurity J by 2,

— *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

— *impurity J*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Limits Spectrophotometer at 210 nm:

— *impurity K*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *any other impurity eluting with a relative retention greater than 1.6*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 10 mL of *glacial acetic acid R* and add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 21.10 mg of $C_{21}H_{32}ClN_5O_2$.

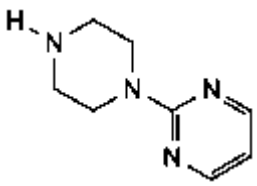
STORAGE

Protected from light.

IMPURITIES

Specified impurities *E, J, K.*

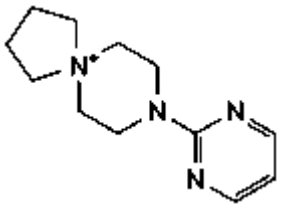
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, F, G, H, I, L, M, N.*



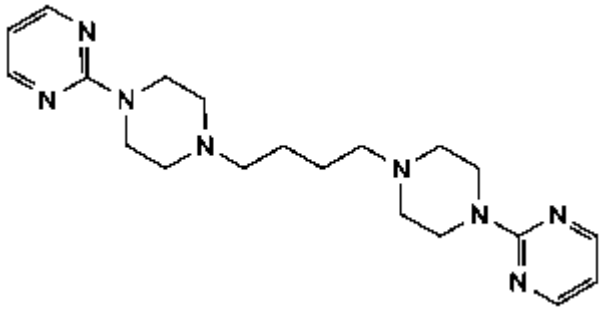
A. 2-(piperazin-1-yl)pyrimidine,

www.webofpharma.com

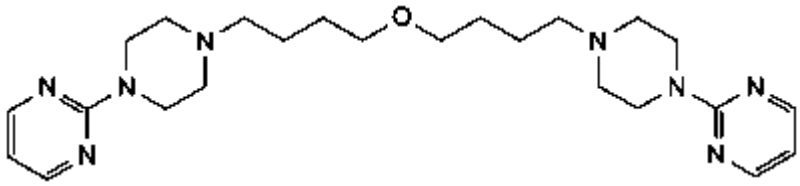
https://thuocngocanh.com/



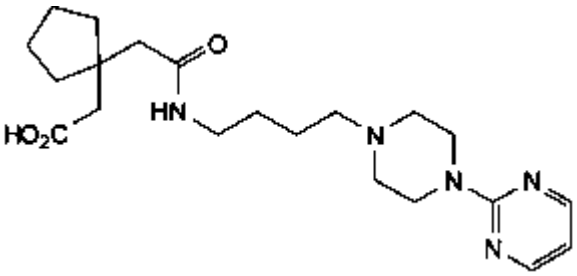
B. 8-(pyrimidin-2-yl)-8-aza-5-azoniaspiro[4.5]decane,



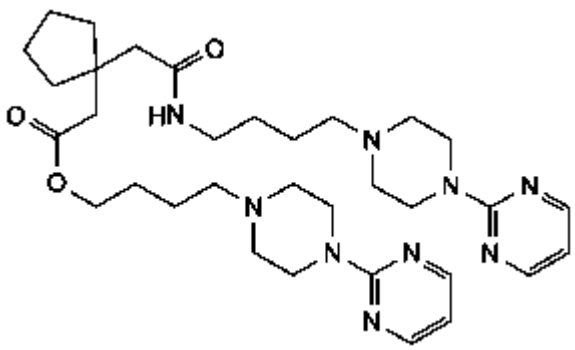
C. 2,2′-[butane-1,4-diylbis(piperazine-1,4-diyl)]dipyrimidine,



D. 2,2′-[oxybis[butane-1,4-diyl(piperazine-1,4-diyl)]]dipyrimidine,

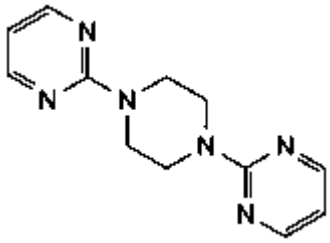


E. [1-[2-oxo-2-[[4-[4-(pyrimidin-2-yl)piperazin-1-yl]butyl]amino]ethyl]cyclopentyl]acetic acid,

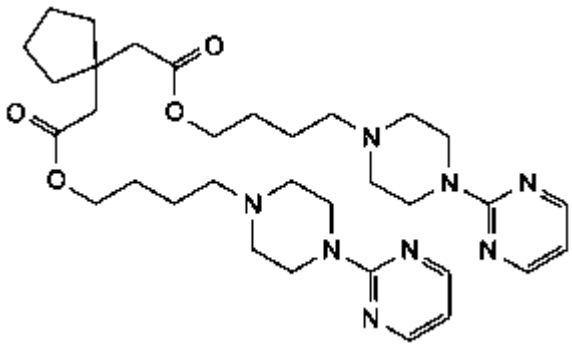


F. 4-[4-(pyrimidin-2-yl)piperazin-1-yl]butyl [1-[2-oxo-2-[[4-[4-(pyrimidin-2-yl)piperazin-1-yl]butyl]amino]ethyl]cyclopentyl]acetate,

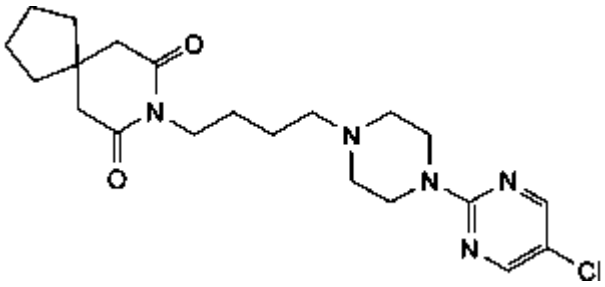
https://thuocngocanh.com/



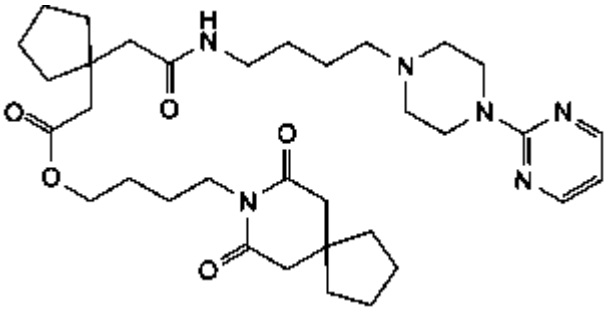
G. 2,2′-(piperazine-1,4-diyl)dipyrimidine,



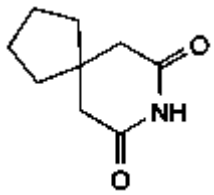
H. bis[4-[4-(pyrimidin-2-yl)piperazin-1-yl]butyl] (cyclopentane-1,1-diyl)diacetate,



I. 8-[4-[4-(5-chloropyrimidin-2-yl)piperazin-1-yl]butyl]-8-azaspiro[4.5]decane-7,9-dione,



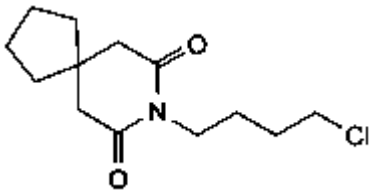
J. 4-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)butyl [1-[2-oxo-2-[[4-[4-(pyrimidin-2-yl)piperazin-1-yl]butyl]amino]ethyl]cyclopentyl]acetate,



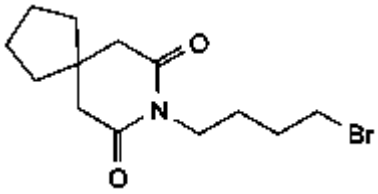
K. 8-azaspiro[4.5]decane-7,9-dione,

www.webofpharma.com

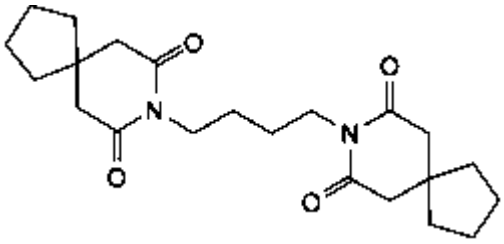
https://thuocngocanh.com/



L. 8-(4-chlorobutyl)-8-azaspiro[4.5]decane-7,9-dione,



M. 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione,



N. 8,8′-(butane-1,4-diyl)bis(8-azaspiro[4.5]decane-7,9-dione).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

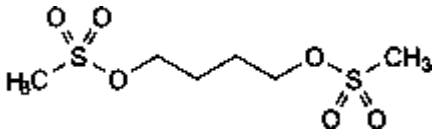
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Busulfan

General Notices

(Ph. Eur. monograph 0542)



$C_6H_{14}O_6S_2$ 246.3 *55-98-1*

Action and use

Cytotoxic alkylating agent.

Preparation

Busulfan Tablets

Ph Eur

DEFINITION

Butane-1,4-diyl di(methanesulfonate).

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in acetone and in acetonitrile, very slightly soluble in ethanol (96 per cent).

mp

About 116 °C.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison busulfan CRS.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 2 mL of acetone R.

Reference solution Dissolve 20 mg of busulfan CRS in 2 mL of acetone R.

Plate TLC silica gel G plate R.

Mobile phase acetone R, toluene R (50:50 *V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In a current of warm air.

Detection Spray with anisaldehyde solution R and heat at 120 °C.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 0.1 g add 5 mL of 1 M sodium hydroxide. Heat until a clear solution is obtained. Allow to cool. To 2 mL of the solution add 0.1 mL of potassium permanganate solution R. The colour changes from purple through violet to blue and finally to green. Filter and add 1 mL of ammoniacal silver nitrate solution R. A precipitate is formed.

D. To 0.1 g add 0.1 g of potassium nitrate R and 0.25 g of sodium hydroxide R, mix and heat to fusion. Allow to cool and dissolve the residue in 5 mL of water R. Adjust to pH 1-2 using dilute hydrochloric acid R. The solution gives reaction (a) of sulfates (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, Method II).

Dissolve 0.25 g in 20 mL of acetonitrile R, dilute to 25 mL with water R and examine immediately.

Acidity

Dissolve 0.20 g with heating in 50 mL of anhydrous ethanol R. Add 0.1 mL of methyl red solution R. Not more than 0.05 mL of 0.1 M sodium hydroxide is required to change the colour of the indicator.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

To 0.250 g add 50 mL of *water R*. Shake. Boil under a reflux condenser for 30 min and, if necessary, make up to the initial volume with *water R*. Allow to cool. Using 0.3 mL of *phenolphthalein solution R* as indicator, titrate with *0.1 M sodium hydroxide* until a pink colour is obtained.

1 mL of *0.1 M sodium hydroxide* is equivalent to 12.32 mg of $C_6H_{14}O_6S_2$.

STORAGE

In an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Busulfan Tablets

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Busulfan Tablets contain Busulfan. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of busulfan, $C_6H_{14}O_6S_2$

90.0 to 115.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 10 mg of Busulfan with 10 mL of hot *acetone*, filter and evaporate the filtrate to dryness. Dry the residue at 60° at a pressure not exceeding 0.7 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of busulfan *(RS 035)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (3) is similar to that of the principal peak in the chromatogram obtained with solution (1).

TESTS

Disintegration

Maximum time, 15 minutes, Appendix XII A1.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Busulfan comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. Prepare a 0.0001% w/v solution of *1,5-di-iodopentane* (internal standard) in *acetone* (solution A).

(1) Add 5 mL of a 30% w/v solution of *sodium iodide* in *acetone* to 5 mL of a 0.0001% w/v solution of *busulfan BPCRS* in *acetone*, stopper the flask lightly and heat in a water bath at 50° for 90 minutes. Cool, add 10 mL of solution A, mix, add 10 mL of *water* and 20 mL of *hexane*, shake vigorously for 1 minute and allow to separate. Use the hexane layer.

(2) Prepare solution (2) in the same manner as solution (3) but using 10 mL of *acetone* in place of solution A.

www.webofpharma.com

https://thietbiuocngocanh.com/

(3) Add 1 mL of *water* to one tablet in a 50 mL graduated flask and mix with the aid of ultrasound until completely dispersed. Add 30 mL of *acetone*, shake for 15 minutes and dilute to 50 mL with *acetone*. Centrifuge and dilute a quantity of the supernatant liquid with *acetone* to produce a solution containing 0.0001% w/v of Busulfan. To 5 mL of the resulting solution add 5 mL of a 30% w/v solution of *sodium iodide* in *acetone*, stopper the flask lightly and heat in a water bath at 50° for 90 minutes. Cool, add 10 mL of solution A, mix, add 10 mL of *water* and 20 mL of *hexane*, shake vigorously for 1 minute and allow to separate. Use the hexane layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed, diatomaceous support* (80 to 100 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable).
(b) Use *helium* as the carrier gas at 1.7 mL per minute.
(c) Use isothermal conditions maintained at 140°.
(d) Use an inlet temperature of 160°.
(e) Use an electron capture detector.
(f) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_{14}O_6S_2$ using the declared content of $C_6H_{14}O_6S_2$ in *busulfan BPCRS*.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. Prepare a 0.0001% w/v solution of *1,5-di-iodopentane* (internal standard) in *acetone* (solution A).

(1) Add 5 mL of a 30% w/v solution of *sodium iodide* in *acetone* to 5 mL of a 0.0001% w/v solution of *busulfan BPCRS* in *acetone*, stopper the flask lightly and heat in a water bath at 50° for 90 minutes. Cool, add 10 mL of solution A, mix, add 10 mL of *water* and 20 mL of *hexane*, shake vigorously for 1 minute and allow to separate. Use the hexane layer.
(2) Prepare solution (2) in the same manner as solution (3) but using 10 mL of *acetone* in place of solution A.
(3) Add 5 mL of *water* to a quantity of powdered tablets containing 2.5 mg of Busulfan and mix with the aid of ultrasound until completely dispersed. Add 150 mL of *acetone*, shake for 15 minutes and dilute to 250 mL with *acetone*. Centrifuge and dilute 10 mL of the supernatant liquid to 100 mL with *acetone*. To 5 mL of the resulting solution add 5 mL of a 30% w/v solution of *sodium iodide* in *acetone*, stopper the flask lightly and heat in a water bath at 50° for 90 minutes. Cool, add 10 mL of solution A, mix, add 10 mL of *water* and 20 mL of *hexane*, shake vigorously for 1 minute and allow to separate. Use the hexane layer.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_{14}O_6S_2$ using the declared content of $C_6H_{14}O_6S_2$ in *busulfan BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

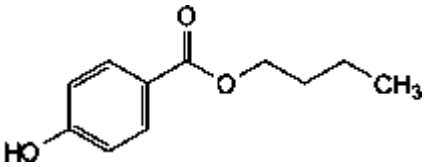
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Butyl Hydroxybenzoate[1]

General Notices

Butylparaben

(Butyl Parahydroxybenzoate, Ph. Eur. monograph 0881)



$C_{11}H_{14}O_3$ 194.2 *94-26-8*

Action and use

Excipient.

Ph Eur

DEFINITION

Butyl 4-hydroxybenzoate.

Content

98.0 per cent to 102.0 per cent.

♦ CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent) and in methanol.♦

IDENTIFICATION

First identification: A, B.

◊ *Second identification: A, C.*◊

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 68 °C to 71 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *butyl parahydroxybenzoate CRS*.

◊ C. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.10 g of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *acetone R*.

Reference solution (a) Dissolve 10 mg of *butyl parahydroxybenzoate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *propyl parahydroxybenzoate R* in 1 mL of test solution (a) and dilute to 10 mL with *acetone R*.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *methanol R* (1:30:70 *V/V/V*).

Application 2 µL of test solution (b) and reference solutions (a) and (b).

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).◊

TESTS

Solution S

Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Acidity

To 2 mL of solution S add 3 mL of *ethanol (96 per cent) R*, 5 mL of *carbon dioxide-free water R* and 0.1 mL of *bromocresol green solution R*. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of methanol R and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of 4-hydroxybenzoic acid R (impurity A), 5 mg of propyl parahydroxybenzoate R (impurity D) and 5 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 50.0 mg of butyl parahydroxybenzoate CRS in 2.5 mL of methanol R and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 5 mg of butyl parahydroxybenzoate impurity E CRS in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (e) Dilute 0.5 mL of reference solution (d) to 50.0 mL with reference solution (b).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 35 °C.

Mobile phase 6.8 g/L solution of potassium dihydrogen phosphate R, methanol R (50:50 *V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 10 µL of the test solution and reference solutions (a), (c) and (e).

Run time 1.5 times the retention time of butyl parahydroxybenzoate.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and D; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity E.

Relative retention With reference to butyl parahydroxybenzoate (retention time = about 22 min): impurity A = about 0.1; impurity D = about 0.5; impurity E = about 0.9.

System suitability:

— resolution:

www.webofpharma.com

https://thuocngocanh.com/

— minimum 5.0 between the peaks due to impurity D and butyl parahydroxybenzoate in the chromatogram obtained with reference solution (a);

— minimum 1.5 between the peaks due to impurity E and butyl parahydroxybenzoate in the chromatogram obtained with reference solution (e).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

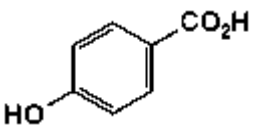
Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{11}H_{14}O_3$ from the declared content of *butyl parahydroxybenzoate CRS*.

IMPURITIES

Specified impurities *A.*

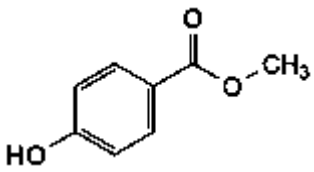
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E.*



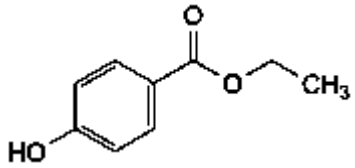
A. 4-hydroxybenzoic acid,

www.webofpharma.com

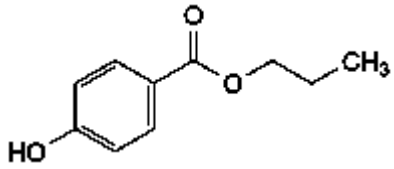
https://thuocngocanh.com/



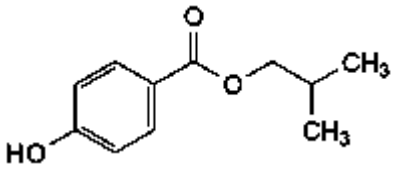
B. methyl 4-hydroxybenzoate (methyl parahydroxybenzoate),



C. ethyl 4-hydroxybenzoate (ethyl parahydroxybenzoate),



D. propyl 4-hydroxybenzoate (propyl parahydroxybenzoate),



E. 2-methylpropyl 4-hydroxybenzoate (iso-butyl parahydroxybenzoate).

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

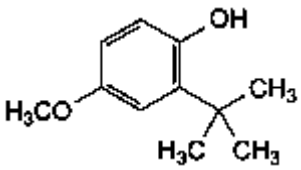
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Butylated Hydroxyanisole

General Notices

(Butylhydroxanisole, Ph. Eur. monograph 0880)



$C_{11}H_{16}O_2$ 180.3 *25013-16-5*

Action and use

Antioxidant.

Ph Eur

DEFINITION

Butylhydroxyanisole is 2-(1,1-dimethylethyl)-4-methoxyphenol containing not more than 10 per cent of 3-(1,1-dimethylethyl)-4-methoxyphenol.

CHARACTERS

A white, yellowish or slightly pinkish, crystalline powder, practically insoluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 per cent) and in fatty oils. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

B. To 0.5 mL of solution S (see Tests) add 10 mL of *4-aminoantipyrine solution R* and 1 mL of *potassium ferricyanide solution R*. Mix and add 10 mL of *methylene chloride R*. Shake vigorously. After separation, the organic layer is red.

C. Dissolve about 10 mg in 2 mL of *ethanol (96 per cent) R*. Add 1 mL of a 1 g/L solution of *testosterone propionate R* in *ethanol (96 per cent) R* and 2 mL of *dilute sodium hydroxide solution R*. Heat in a water-bath at 80 °C for 10 min and allow to cool. A red colour develops.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 2.5 g in *ethanol (96 per cent) R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a) Dissolve 0.25 g of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methylene chloride R*.

Reference solution (a) Dissolve 25 mg of *butylhydroxyanisole CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1 mL of reference solution (a) to 20 mL with *methylene chloride R*.

Reference solution (c) Dissolve 50 mg of *hydroquinone R* in 5 mL of *ethanol (96 per cent) R* and dilute to 100 mL with *methylene chloride R*. Dilute 1 mL of this solution to 10 mL with *methylene chloride R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 10 cm using *methylene chloride R*. Allow the plate to dry in air and spray with a freshly prepared mixture of 10 volumes of *potassium ferricyanide solution R*, 20 volumes of *ferric chloride solution R1* and 70 volumes of *water R*. In the chromatogram obtained with test solution (a): any violet-blue spot with an R_F value of about 0.35 (corresponding to 3-(1,1-dimethylethyl)-4-methoxyphenol) is not more intense than the principal spot in the chromatogram obtained with reference solution (a) (10 per cent); any spot corresponding to hydroquinone is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.2 per cent); any spot, apart from the principal spot and any spots corresponding to 3-(1,1-dimethylethyl)-4-methoxyphenol and hydroquinone, is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

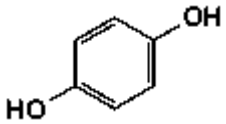
Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

STORAGE

Store protected from light.

IMPURITIES



A. benzene-1,4-diol (hydroquinone).

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

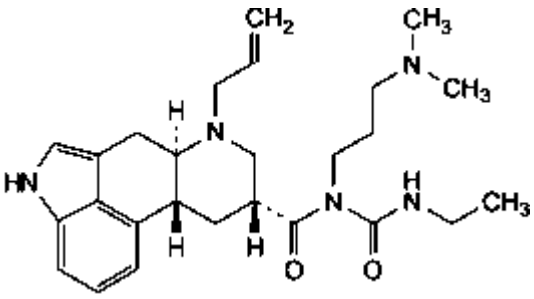
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cabergoline

General Notices

(Ph. Eur. monograph 1773)



$C_{26}H_{37}N_5O_2$ 451.6 *81409-90-7*

Action and use

Dopamine D2 receptor agonist.

Preparation

Cabergoline Tablets

Ph Eur

DEFINITION

1-Ethyl-3-[3-(dimethylamino)propyl]-3-[[(6a*R*,9*R*,10a*R*)-7-(prop-2-enyl)-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinolin-9-yl]carbonyl]urea.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, freely soluble in ethanol (96 per cent), very slightly soluble in hexane. It is slightly soluble in 0.1 M hydrochloric acid.

It shows polymorphism (5.9).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *cabergoline CRS*.

If the spectra obtained in the solid state show differences, dissolve 50 mg of the substance to be examined and 50 mg of the reference substance separately in 1 mL of *ethanol (96 per cent) R*, evaporate to dryness and record new spectra using the residues.

TESTS

Specific optical rotation (2.2.7)

-77 to -83 (anhydrous substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protected from light.*

Test solution Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 30.0 mg of *cabergoline CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) Suspend 50 mg of the substance to be examined in 10 mL of *0.1 M sodium hydroxide*. Stir for about 15 min. To 1 mL of the suspension add 1 mL of *0.1 M hydrochloric acid* and dilute to 10 mL with the mobile phase. Sonicate until dissolution is complete. The main degradation product obtained is impurity A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase Mix 16 volumes of *acetonitrile R* and 84 volumes of a freshly prepared 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.0 with *phosphoric acid R*. Add 0.2 volumes of *triethylamine R*.

Flow rate 1.2 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 280 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 4 times the retention time of cabergoline.

Relative retention With reference to cabergoline (retention time = about 12 min): impurity D = about 0.3; impurity B = about 0.6; impurity A = about 0.8; impurity C = about 2.9.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to cabergoline and impurity A.

Limits:

— *impurities A, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities B, D*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.000 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{26}H_{37}N_5O_2$ from the areas of the peaks and the declared content of *cabergoline CRS*.

STORAGE

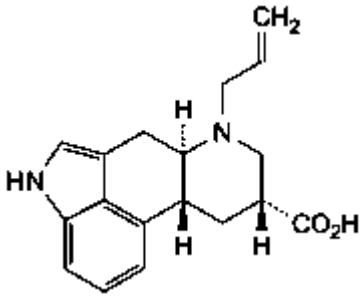
Protected from light.

IMPURITIES

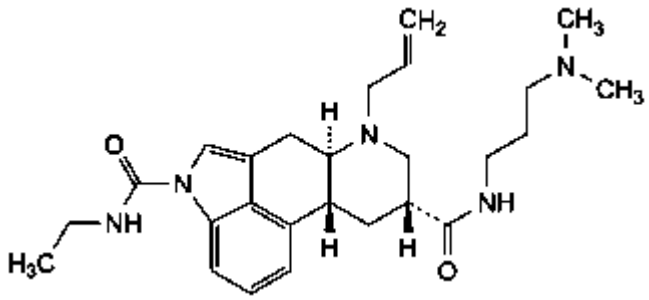
Specified impurities *A, B, C, D.*

www.webofpharma.com

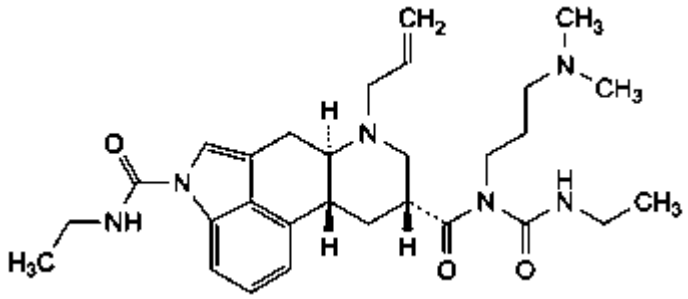
https://thuocngocanh.com/



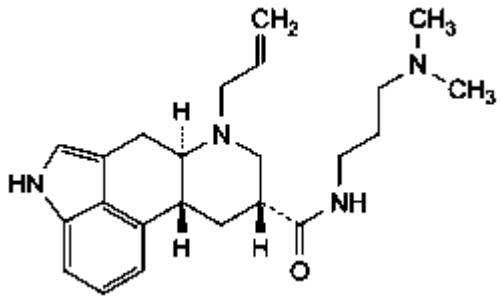
A. (6a*R*,9*R*,10a*R*)-7-(prop-2-enyl)-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid,



B. (6a*R*,9*R*,10a*R*)-N^9-[3-(dimethylamino)propyl]-N^4-ethyl-7-(prop-2-enyl)-6a,7,8,9,10,10a-hexahydroindolo[4,3-*fg*]quinoline-4,9(6*H*)-dicarboxamide,



C. (6a*R*,9*R*,10a*R*)-N^9-[3-(dimethylamino)propyl]-N^4-ethyl-N^9-(ethylcarbamoyl)-7-(prop-2-enyl)-6a,7,8,9,10,10a-hexahydroindolo[4,3-*fg*]quinoline-4,9(6*H*)-dicarboxamide,



D. (6a*R*,9*R*,10a*R*)-*N*-[3-(dimethylamino)propyl]-7-(prop-2-enyl)-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cabergoline Tablets

General Notices

Action and use

Dopamine D_2 receptor agonist.

DEFINITION

Cabergoline Tablets contain Cabergoline.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of cabergoline, $C_{26}H_{37}N_5O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 400 nm of solution (1) in the Assay is concordant with that obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 15 minutes withdraw a sample of the medium and filter. Dilute the filtrate with dissolution medium, if necessary, to produce a solution expected to contain 0.0001% w/v of Cabergoline.

(2) 0.0001% w/v of *cabergoline EPCRS* in the dissolution medium.

(3) Suspend 25 mg of *cabergoline EPCRS* in 5 mL of 0.1M sodium hydroxide. Stir for about 15 minutes. To 1 mL of the suspension add 1 mL of 0.1M *hydrochloric acid* and dilute to 10 mL with the mobile phase. Mix with the aid of ultrasound until dissolution is complete and

www.webofpharma.com

https://thietbiuocngocanh.com/

dilute 1 volume of this solution to 5 volumes with the mobile phase (*in-situ* degradation of cabergoline to produce impurity A).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

0.2 volumes of *triethylamine*, 16 volumes of *acetonitrile* and 84 volumes of a freshly prepared 0.68% w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 2.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to cabergoline (retention time, about 12 minutes) are: impurity D, about 0.3; impurity B, about 0.6; impurity A, about 0.8; impurity C, about 2.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cabergoline and impurity A is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{37}N_5O_2$ in each tablet from the chromatograms obtained and using the declared content of $C_{26}H_{37}N_5O_2$ in *cabergoline EPCRS*.

LIMITS

The amount of cabergoline released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 2.5 mg of Cabergoline with 7 mL of the mobile phase, add sufficient mobile phase to produce 10 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Suspend 25 mg of *cabergoline EPCRS* in 5 mL of 0.1M *sodium hydroxide*. Stir for about 15 minutes. To 1 mL of the suspension add 1 mL of 0.1M *hydrochloric acid* and dilute to 10 mL with the mobile phase. Mix with the aid of ultrasound until dissolution is complete and dilute 1 volume of this solution to 5 volumes with the mobile phase (*in-situ* degradation of cabergoline to produce impurity A).

(4) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thietbiuocngocanh.com/

The chromatographic conditions described under Dissolution may be used. For solution (1), allow the chromatography to run for four times the retention time of the peak due to cabergoline.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to cabergoline (retention time, about 12 minutes) are: impurity D, about 0.3; impurity B, about 0.6; impurity A, about 0.8; impurity C, about 2.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cabergoline and impurity A is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A or impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of cabergoline comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse one tablet with the aid of ultrasound in 3 mL of the mobile phase. Allow to cool, add sufficient of the mobile phase to produce a solution expected to contain 0.025% w/v of Cabergoline and filter.
(2) 0.025% w/v of *cabergoline EPCRS* in the mobile phase.
(3) Suspend 25 mg of *cabergoline EPCRS* in 5 mL of 0.1M *sodium hydroxide*. Stir for about 15 minutes. To 1 mL of the suspension add 1 mL of 0.1M *hydrochloric acid* and dilute to 10 mL with the mobile phase. Mix with the aid of ultrasound until dissolution is complete and dilute 1 volume of this solution to 5 volumes with the mobile phase (*in-situ* degradation of cabergoline to produce impurity A).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, with an injection volume of 250 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cabergoline and impurity A is at least 3.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thietbiuocngocanh.com/

Calculate the content of $C_{26}H_{37}N_5O_2$ in each tablet from the chromatograms obtained and using the declared content of $C_{26}H_{37}N_5O_2$ in *cabergoline EPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of cabergoline

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of cabergoline

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 2.5 mg of Cabergoline with 7 mL of the mobile phase, add sufficient mobile phase to produce 10 mL and filter.

(2) 0.025% w/v of *cabergoline EPCRS* in the mobile phase.

(3) Suspend 25 mg of *cabergoline EPCRS* in 5 mL of 0.1M *sodium hydroxide*. Stir for about 15 minutes. To 1 mL of the suspension add 1 mL of 0.1M *hydrochloric acid* and dilute to 10 mL with the mobile phase. Mix with the aid of ultrasound until dissolution is complete and dilute 1 volume of this solution to 5 volumes with the mobile phase (*in-situ* degradation of cabergoline to produce impurity A).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cabergoline and impurity A is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{37}N_5O_2$ in the tablets from the chromatograms obtained and using the declared content of $C_{26}H_{37}N_5O_2$ in *cabergoline EPCRS*.

STORAGE

Cabergoline Tablets should be stored in accordance with the manufacturers instruction.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Cabergoline.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

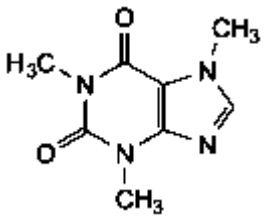
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Caffeine

General Notices

Anhydrous Caffeine

(Ph. Eur. monograph 0267)



$C_8H_{10}N_4O_2$ 194.2 *58-08-2*

Action and use

Central nervous system stimulant.

Preparations

Aspirin and Caffeine Tablets

Caffeine Citrate Injection

Caffeine Citrate Oral Solution

Paracetamol and Caffeine Capsules

Paracetamol and Caffeine Tablets

Paracetamol, Codeine Phosphate and Caffeine Capsules

Paracetamol, Codeine Phosphate and Caffeine Tablets

Ph Eur

DEFINITION

1,3,7-Trimethyl-3,7-dihydro-1*H*-purine-2,6-dione.

Content

98.5 per cent to 101.5 per cent (dried substance).

www.webofpharma.com

https://thuocngocanh.com/

CHARACTERS

Appearance

White or almost white, crystalline powder or silky crystals.

Solubility

Sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol (96 per cent). It dissolves in concentrated solutions of alkali benzoates or salicylates.

It sublimes readily.

IDENTIFICATION

First identification: A, B, E.

Second identification: A, C, D, E, F.

A. Melting point (2.2.14): 234 °C to 239 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *caffeine CRS*.

C. To 2 mL of a saturated solution add 0.05 mL of *iodinated potassium iodide solution R*. The solution remains clear. Add 0.1 mL of *dilute hydrochloric acid R*; a brown precipitate is formed. Neutralise with *dilute sodium hydroxide solution R*; the precipitate dissolves.

D. In a ground-glass-stoppered tube, dissolve about 10 mg in 0.25 mL of a mixture of 0.5 mL of *acetylacetone R* and 5 mL of *dilute sodium hydroxide solution R*. Heat in a water-bath at 80 °C for 7 min. Cool and add 0.5 mL of *dimethylaminobenzaldehyde solution R2*. Heat again in a water-bath at 80 °C for 7 min. Allow to cool and add 10 mL of *water R*; an intense blue colour develops.

E. Loss on drying (see Tests).

F. It gives the reaction of xanthines (2.3.1).

TESTS

Solution S

Dissolve 0.5 g with heating in 30 mL of *carbon dioxide-free water R* prepared from *distilled water R*, cool and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity

www.webofpharma.com

https://thuocngocanh.com/

To 10 mL of solution S add 0.05 mL of *bromothymol blue solution R1*; the solution is green or yellow. Not more than 0.2 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *caffeine for system suitability CRS* (containing impurities A, C, D and F) in the mobile phase and dilute to 5 mL with the mobile phase. Dilute 2 mL of this solution to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped amidohexadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 20 volumes of *tetrahydrofuran R*, 25 volumes of *acetonitrile R* and 955 volumes of a solution containing 0.82 g/L of *anhydrous sodium acetate R* previously adjusted to pH 4.5 with *glacial acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL.

Run time 1.5 times the retention time of caffeine.

Identification of impurities Use the chromatogram supplied with *caffeine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, C, D and F.

Relative retention With reference to caffeine (retention time = about 8 min): impurity C = about 0.38; impurity D = about 0.42; impurity F = about 0.6; impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities C and D and minimum 2.5 between the peaks due to impurities F and A.

Limits:

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulfates (2.4.13)

Maximum 500 ppm, determined on 15 mL of solution S.

Prepare the standard using a mixture of 7.5 mL of *sulfate standard solution (10 ppm SO_4) R* and 7.5 mL of *distilled water R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

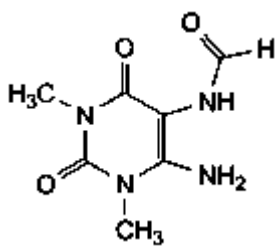
Dissolve 0.170 g with heating in 5 mL of *anhydrous acetic acid R*. Allow to cool, add 10 mL of *acetic anhydride R* and 20 mL of *toluene R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 19.42 mg of $C_8H_{10}N_4O_2$.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F.

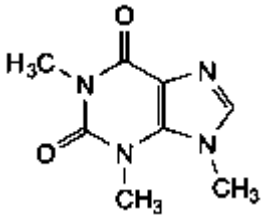
A. 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theophylline),



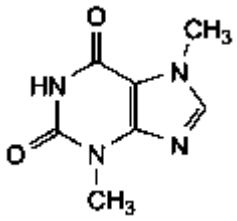
www.webofpharma.com

https://thuocngocanh.com/

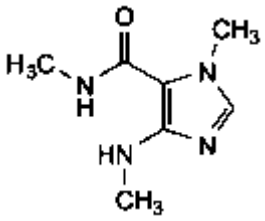
B. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



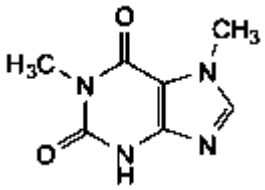
C. 1,3,9-trimethyl-3,9-dihydro-1*H*-purine-2,6-dione (isocaffeine),



D. 3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theobromine),



E. *N*,1-dimethyl-4-(methylamino)-1*H*-imidazole-5-carboxamide (caffeidine),



F. 1,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Caffeine Citrate Injection

General Notices

Action and use

Respiratory and central nervous system stimulant.

DEFINITION

Caffeine Citrate Injection is a sterile solution of caffeine citrate, prepared by the interaction of Caffeine and Citric Acid Monohydrate, in Water for Injections. Sodium citrate may also be present.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of caffeine citrate, $C_8H_{10}N_4O_2,C_6H_8O_7$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions preparing a mixture containing 2 volumes of *methanol* and 3 volumes of *dichloromethane*.

(1) Dilute a volume of the injection containing the equivalent of 10 mg of caffeine to 100 mL.

(2) 0.01% w/v of *caffeine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light* (254 nm).

MOBILE PHASE

1 volume of *concentrated ammonia*, 3 volumes of *acetone*, 3 volumes of *dichloromethane* and 4 volumes of *butan-1-ol*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. Yields the reaction characteristic of *citrates*, Appendix VI.

TESTS

Acidity

pH, 2.0 to 5.2, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a volume of the injection containing the equivalent of 50 mg caffeine to 250 mL and filter through a 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 5 volumes.

(3) 0.02% w/v each of *theobromine*, *1,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione* (impurity F), *theophylline BPCRS* and *caffeine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5µm) (Waters C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 10 µL of each solution.

(g) Continue the chromatography for about 25 minutes.

MOBILE PHASE

4 volumes of *tetrahydrofuran*, 5 volumes of *acetonitrile* and 191 volumes of 0.01M *anhydrous sodium acetate*, previously adjusted to pH 4.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), there are 4 distinct peaks and the *resolution* between the peaks due to theophylline and caffeine is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

www.webofpharma.com

https://thietbiuocngocanh.com/

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a volume of the injection containing the equivalent of 50 mg caffeine to 250 mL and filter through a 0.45-µm filter.

(2) 0.02% w/v of *caffeine BPCRS*.

(3) 0.02% w/v each of *theobromine*, *1,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione*, *theophylline BPCRS* and *caffeine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, the chromatogram obtained with solution (3) has four distinct peaks and the *resolution* between the peaks due to theophylline and caffeine is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{10}N_4O_2,C_6H_8O_7$ in the injection using the declared content of $C_8H_{10}N_4O_2$ in *caffeine BPCRS*. Each mg of $C_8H_{10}N_4O_2$ is equivalent to 1.989 mg of $C_8H_{10}N_4O_2,C_6H_8O_7$.

LABELLING

The label states the quantity of active ingredient in terms of the amount of caffeine citrate and the equivalent amount of caffeine.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C, D and F listed under Caffeine.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Caffeine Citrate Oral Solution

General Notices

Action and use

Respiratory and central nervous system stimulant.

DEFINITION

Caffeine Citrate Oral Solution is a solution of caffeine citrate, prepared by the interaction of Caffeine and Citric Acid Monohydrate, in a suitable aqueous vehicle. Sodium citrate may also be present.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of caffeine citrate, $C_8H_{10}N_4O_2,C_6H_8O_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solution preparing a mixture containing 2 volumes of *methanol* and 3 volumes of *dichloromethane*.

(1) Dilute a volume of the oral solution containing the equivalent of 10 mg of caffeine to 100 mL.

(2) 0.01% w/v of *caffeine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light* (254 nm).

MOBILE PHASE

1 volume of *concentrated ammonia*, 3 volumes of *acetone*, 3 volumes of *dichloromethane* and 4 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thietbiuocngocanh.com/

C. Yields the reaction characteristic of *citrates*, Appendix VI.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a volume of the oral solution containing the equivalent of 50 mg caffeine to 250 mL and filter through a 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 5 volumes.

(3) 0.02% w/v each of *theobromine*, *1,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione* (impurity F), *theophylline BPCRS* and *caffeine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5µm) (Waters C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

4 volumes of *tetrahydrofuran*, 5 volumes of *acetonitrile* and 191 volumes of 0.01M *anhydrous sodium acetate*, previously adjusted to pH 4.5 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, the chromatogram obtained with solution (3) has 4 distinct peaks and the *resolution* between the peaks due to theophylline and caffeine is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a volume of the oral solution containing the equivalent of 50 mg caffeine to 250 mL and filter through a 0.45-µm filter.

(2) 0.02% w/v of *caffeine BPCRS*.

(3) 0.02% w/v each of *theobromine*, *1,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione*, *theophylline BPCRS* and *caffeine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, the chromatogram obtained with solution (3) has 4 distinct peaks and the *resolution* between the peaks due to theophylline and caffeine is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{10}N_4O_2,C_6H_8O_7$ in the oral solution using the declared content of $C_8H_{10}N_4O_2$ in *caffeine BPCRS*. Each mg of $C_8H_{10}N_4O_2$ is equivalent to 1.989 mg of $C_8H_{10}N_4O_2,C_6H_8O_7$

LABELLING

The quantity of active ingredient is stated in terms of the amount of caffeine citrate and the equivalent amount of caffeine.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C, D and F listed under Caffeine.

© Crown Copyright 2022

www.webofpharma.com

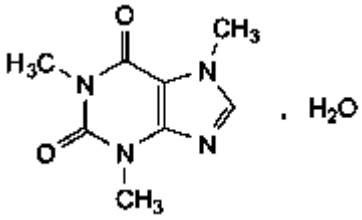
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Caffeine Hydrate

General Notices

(Caffeine Monohydrate, Ph. Eur. monograph 0268)



$C_8H_{10}N_4O_2,H_2O$ 212.2 *5743-12-4*

Action and use

Central nervous system stimulant.

Ph Eur

DEFINITION

1,3,7-Trimethyl-3,7-dihydro-1*H*-purine-2,6-dione monohydrate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or silky crystals.

Solubility

Sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol (96 per cent). It dissolves in concentrated solutions of alkali benzoates or salicylates.

It sublimes readily.

IDENTIFICATION

First identification: A, B, E.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, C, D, E, F.

A. Melting point (2.2.14): 234 °C to 239 °C, determined after drying at 100-105 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Dry the substance to be examined at 100-105 °C before use.

Comparison *caffeine CRS*.

C. To 2 mL of a saturated solution add 0.05 mL of *iodinated potassium iodide solution R*; the solution remains clear. Add 0.1 mL of *dilute hydrochloric acid R*; a brown precipitate is formed. Neutralise with *dilute sodium hydroxide solution R*; the precipitate dissolves.

D. In a glass-stoppered tube, dissolve about 10 mg in 0.25 mL of a mixture of 0.5 mL of *acetylacetone R* and 5 mL of *dilute sodium hydroxide solution R*. Heat in a water-bath at 80 °C for 7 min. Cool and add 0.5 mL of *dimethylaminobenzaldehyde solution R2*. Heat again in a water-bath at 80 °C for 7 min. Allow to cool and add 10 mL of *water R*; an intense blue colour develops.

E. Loss on drying (see Tests).

F. It gives the reaction of xanthines (2.3.1).

TESTS

Solution S

Dissolve 0.5 g with heating in 30 mL of *carbon dioxide-free water R* prepared from *distilled water R*, cool, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

Acidity

To 10 mL of solution S add 0.05 mL of *bromothymol blue solution R1*; the solution is green or yellow. Not more than 0.2 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.110 g of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *caffeine for system suitability CRS* (containing impurities A, C, D and F) in the mobile phase and dilute to 5 mL with the mobile phase. Dilute 2 mL of this solution to 10 mL with the mobile phase.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped amidohexadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 20 volumes of *tetrahydrofuran R*, 25 volumes of *acetonitrile R* and 955 volumes of a solution containing 0.82 g/L of *anhydrous sodium acetate R* previously adjusted to pH 4.5 with *glacial acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL.

Run time 1.5 times the retention time of caffeine.

Identification of impurities Use the chromatogram supplied with *caffeine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, C, D and F.

Relative retention With reference to caffeine (retention time = about 8 min): impurity C = about 0.38; impurity D = about 0.42; impurity F = about 0.6; impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities C and D; minimum 2.5 between the peaks due to impurities F and A.

Limits:

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulfates (*2.4.13*)

Maximum 500 ppm, determined on 15 mL of solution S.

Prepare the standard using a mixture of 7.5 mL of *sulfate standard solution (10 ppm SO_4) R* and 7.5 mL of *distilled water R*.

Loss on drying (*2.2.32*)

5.0 per cent to 9.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 1 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

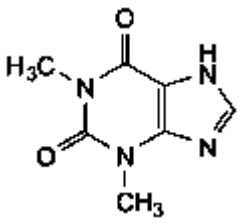
https://thuocngocanh.com/

Dissolve 0.170 g, previously dried at 100-105 °C, with heating in 5 mL of *anhydrous acetic acid R*. Allow to cool, and add 10 mL of *acetic anhydride R* and 20 mL of *toluene R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

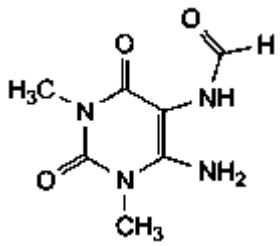
1 mL of *0.1 M perchloric acid* is equivalent to 19.42 mg of $C_8H_{10}N_4O_2$.

IMPURITIES

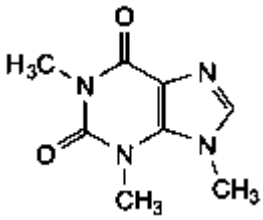
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F.



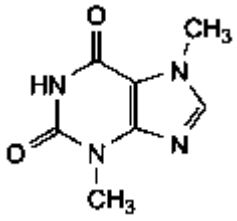
A. 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theophylline),



B. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



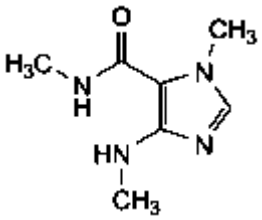
C. 1,3,9-trimethyl-3,9-dihydro-1*H*-purine-2,6-dione (isocaffeine),



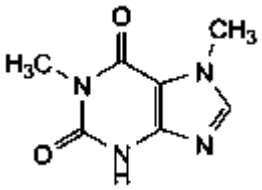
D. 3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theobromine),

www.webofpharma.com

https://thuocngocanh.com/



E. *N*,1-dimethyl-4-(methylamino)-1*H*-imidazole-5-carboxamide (caffeidine),



F. 1,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calamine

General Notices

Prepared Calamine

Action and use

Antipruritic.

Preparations

Aqueous Calamine Cream

Calamine Lotion

Calamine Ointment

Calamine and Coal Tar Ointment

DEFINITION

Calamine is a basic zinc carbonate suitably coloured with iron(III) oxide.

CHARACTERISTICS

An amorphous, impalpable, pink or reddish brown powder, the colour depending on the variety and amount of iron(III) oxide present and the process by which it is incorporated.

Practically insoluble in *water*. It dissolves with effervescence in *hydrochloric acid*.

IDENTIFICATION

A. Yields the reactions characteristic of *carbonates*, Appendix VI.

B. To 2 g add 5 mL of *hydrochloric acid* and heat to boiling; if necessary, add *hydrochloric acid* drop wise until a bright yellow solution is obtained. Cool and add *13.5M ammonia* until the first sign of precipitate (solution A). The solution yields reaction B characteristic of *iron salts*, Appendix VI. Dilute 1 mL of solution A to 5 mL with *water*; the solution yields the reaction characteristic of *zinc salts*, Appendix VI.

TESTS

Calcium

Dissolve 0.50 g in a mixture of 10 mL of *water* and 2.5 mL of *glacial acetic acid* and filter. To 0.5 mL of the filtrate add 15 mL of *5M ammonia* and 2 mL of a 2.5% w/v solution of *ammonium oxalate* and allow to stand for 2 minutes. The solution remains clear.

www.webofpharma.com

https://thuocngocanh.com/

Soluble barium salts

To the remainder of the filtrate obtained in the test for Calcium add 2 mL of *1M sulfuric acid* and allow to stand for 5 minutes. The solution remains clear.

Lead

Not more than 150 ppm when determined by *atomic absorption spectrophotometry*, Appendix II D, Method II, measuring at 283.3 nm or 217 nm and using an air-acetylene flame. Carefully add 5 g of the substance being examined to 25 mL of *hydrochloric acid* and allow to stand for 18 hours. Add 5 mL of *nitric acid* and sufficient *water* to produce 200 mL. Use *lead standard solution (100 ppm Pb)* suitably diluted with a 3.5% v/v solution of *nitric acid* to prepare the standard solution.

Chloride

Dissolve 0.15 g in *water* with the addition of 1 mL of *nitric acid*, filter and dilute to 30 mL with *water*. The resulting solution complies with the *limit test for chlorides*, Appendix VII (0.07%).

Sulfate

Dissolve 0.1 g in *water* with the addition of 3 mL of *2M hydrochloric acid*, filter and dilute to 60 mL with *water*. The resulting solution complies with the *limit test for sulfates*, Appendix VII (0.6%).

Ethanol-soluble dyes

Shake 1.0 g with 10 mL of *ethanol (90%)* and filter. The filtrate is *colourless*, Appendix IV B, Method II.

Matter insoluble in hydrochloric acid

Dissolve 1 g in 20 mL of warm *2M hydrochloric acid* and filter. The residue, when washed with *water* and dried to constant weight at 105°, weighs not more than 10 mg.

Water-soluble dyes

Shake 1.0 g with 10 mL of *water* and filter. The filtrate is *colourless*, Appendix IV B, Method II.

Residue on ignition

68.0 to 74.0%, when ignited at a temperature not lower than 900° until, after further ignition, two successive weighings do not differ by more than 0.2% of the weight of the residue. Use 1 g.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calamine and Coal Tar Ointment

General Notices

Compound Calamine Ointment

DEFINITION

Calamine and Coal Tar Ointment contains 12.5% w/w each of Calamine and Zinc Oxide and 2.5% w/w of Strong Coal Tar Solution in a suitable water-emulsifying basis.

Extemporaneous preparation

The following formula and directions apply.

Calamine, finely sifted	125 g
Zinc Oxide, finely sifted	125 g
Strong Coal Tar Solution	25 g
Hydrous Wool Fat	250 g
White Soft Paraffin	475 g

Melt together the Hydrous Wool Fat and the White Soft Paraffin. Triturate the Calamine and Zinc Oxide in the melted basis and stir gently, when cooled, to about 40°. Gradually incorporate the Strong Coal Tar Solution and stir until cold.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc compounds, calculated as ZnO

19.8 to 22.8% w/w.

IDENTIFICATION

The residue obtained in the Assay is yellow when hot and white when cool.

ASSAY

Gently heat 1 g until the basis is completely volatilised or charred. Increase the heat until the carbon is removed and ignite the residue of ZnO until, after further ignition, two successive weighings do not differ by more than 0.2% of the weight of the residue. Each g of residue is equivalent to 0.8034 g of Zn.

STORAGE

www.webofpharma.com

https://thietbiuocngocanh.com/

Calamine and Coal Tar Ointment should be kept in a container that minimises evaporation losses.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calamine Lotion

General Notices

Calamine Cutaneous Suspension

DEFINITION

Calamine Lotion is a *cutaneous suspension*.

Calamine	150 g
Zinc Oxide	50 g
Bentonite	30 g
Sodium Citrate	5 g
Liquefied Phenol	5 mL
Glycerol	50 mL
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

Extemporaneous preparation

The following directions apply.

Triturate the Calamine, the Zinc Oxide and the Bentonite with a solution of the Sodium Citrate in about 700 mL of the Purified Water and add the Liquefied Phenol, the Glycerol and sufficient Purified Water to produce 1000 mL.

The lotion complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

IDENTIFICATION

A. To 2 mL add 2 mL of *periodic acid reagent*, shake, centrifuge and add 0.5 mL of the supernatant liquid to 2 mL of *ammoniacal silver nitrate solution* in a test tube. Heat on a water bath at 70° for 5 minutes. A silver mirror is produced on the side of the tube.

B. Mix 2 mL with 50 mL of *water*, centrifuge and decant the supernatant liquid. Suspend the residue in 20 mL of *water*, add 1 mL of *hydrochloric acid*, mix and filter. 5 mL of the filtrate, after neutralisation by drop wise addition of 2M *sodium hydroxide*, yields the reaction characteristic of *zinc salts*, Appendix VI.

Residue on ignition

14.5 to 18.0% w/w when determined by the following method. Evaporate 5 g to dryness and ignite until, after further ignition, two successive weighings do not differ by more than 0.2% of the weight of the residue.

www.webofpharma.com

https://thietkeuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products
Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calamine Ointment

General Notices

DEFINITION

Calamine Ointment contains 15% w/w of Calamine in a suitable hydrophobic basis.

Extemporaneous preparation

The following formula and directions apply.

Calamine, finely sifted	150 g
White Soft Paraffin	850 g

Triturate the Calamine with part of the White Soft Paraffin until smooth and gradually incorporate the remainder of the White Soft Paraffin.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of zinc, Zn

7.8 to 9.4% w/w.

IDENTIFICATION

The residue obtained in the Assay is yellow when hot and white when cool.

ASSAY

Gently heat 1 g until the basis is completely volatilised or charred, increase the heat until all the carbon is removed and ignite the residue until, after further ignition, two successive weighings do not differ by more than 0.2% of the weight of the residue. Each g of residue is equivalent to 0.8034 g of Zn.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thietkeuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

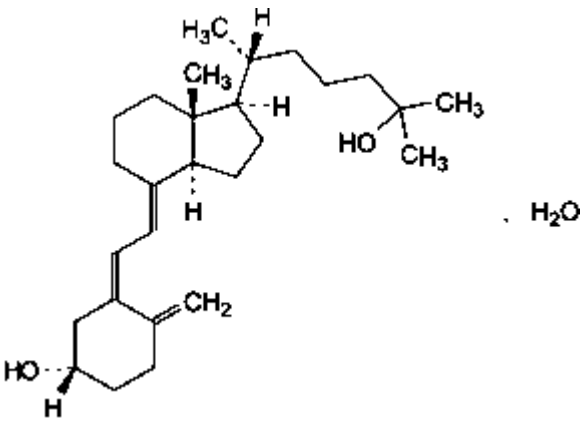
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcifediol Monohydrate

General Notices

Calcifediol

(Ph. Eur. monograph 1295)



$C_{27}H_{44}O_2,H_2O$ 418.7 *63283-36-3*

Action and use

Vitamin D analogue.

Ph Eur

DEFINITION

(3*S*,5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-3,25-diol monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

A reversible isomerisation to pre-calcifediol takes place in solution, depending on temperature and time. The activity is due to both compounds (see Assay).

CHARACTERS

Appearance

White or almost white crystals.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in fatty oils.

It is sensitive to air, heat and light.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of calcifediol*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Carry out the test as rapidly as possible, avoiding exposure to actinic light and air.*

Test solution Dissolve 5.0 mg of the substance to be examined without heating in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *calcifediol CRS* without heating in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Heat 2 mL of reference solution (a) in a water-bath at 80 °C under a reflux condenser for 2 h and cool.

Reference solution (d) Dissolve 1 mg of *calcifediol for impurity D identification CRS* in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *methanol R* (20:80 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 50 µL of the test solution and reference solutions (b), (c) and (d).

www.webofpharma.com

https://thuocngocanh.com/

Run time Twice the retention time of calcifediol.

Identification of impurities Use the chromatogram supplied with *calcifediol for impurity D identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity D.

Relative retention With reference to calcifediol (retention time = about 11 min): pre-calcifediol = about 1.3; impurity D = about 1.7.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to calcifediol and pre-calcifediol.

Limits:

— *impurity D*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent (0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b)); disregard the peak due to pre-calcifediol.

Water (*2.5.32*)

3.8 per cent to 5.0 per cent, determined on 10.0 mg by direct introduction of the sample.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{27}H_{44}O_2$ taking into account the assigned content of *calcifediol CRS* and, if necessary, the peak due to pre-calcifediol.

STORAGE

Under nitrogen, in an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

The contents of an opened container are to be used immediately.

IMPURITIES

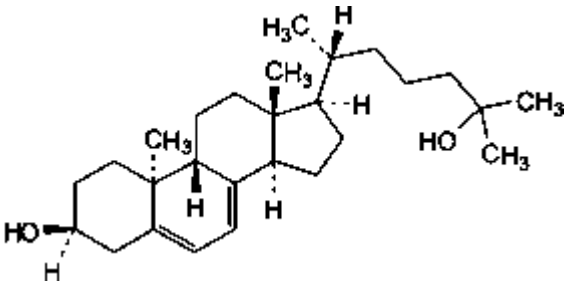
Specified impurities *D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

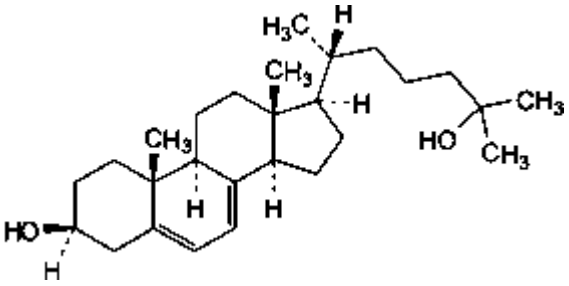
www.webofpharma.com

https://thuocngocanh.com/

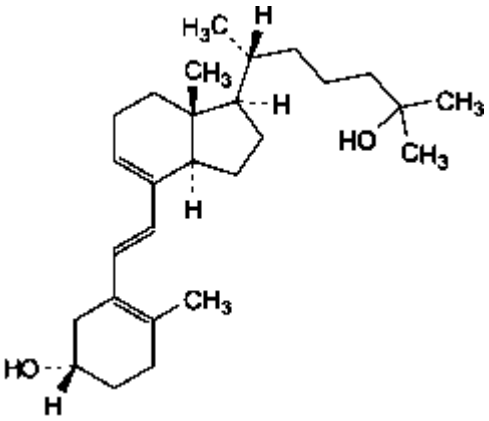
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.



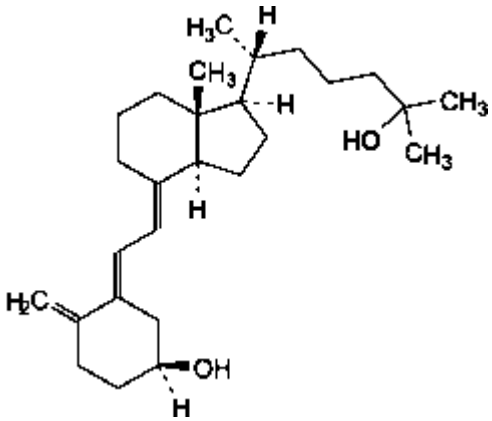
A. 9β,10α-cholesta-5,7-diene-3β,25-diol,



B. cholesta-5,7-diene-3β,25-diol,



C. (3*S*,6*E*)-9,10-secocholesta-5(10),6,8-triene-3,25-diol,



www.webofpharma.com

https://nhathuocngocanh.com/

D. (3*S*,5*E*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-3,25-diol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

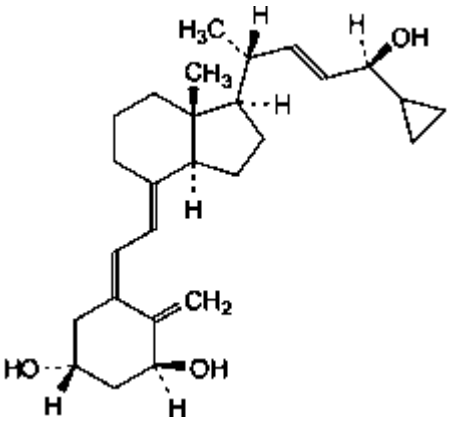
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcipotriol

General Notices

Anhydrous Calcipotriol

(Ph. Eur. monograph 2011)



$C_{27}H_{40}O_3$ 412.6 *112965-21-6*

Action and use

Vitamin D analogue.

Preparations

Calcipotriol and Betamethasone Cutaneous Foam

Calcipotriol and Betamethasone Gel

Calcipotriol and Betamethasone Ointment

Calcipotriol Cream

Calcipotriol Ointment

Calcipotriol Scalp Application

Ph Eur

DEFINITION

(5*Z*,7*E*,22*E*,24*S*)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol.

Content

www.webofpharma.com

https://thuocngocanh.com/

95.5 per cent to 102.0 per cent (dried substance).

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

It is sensitive to heat and light.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of anhydrous calcipotriol*.

B. Loss on drying (see Tests).

TESTS

Carry out the tests for related substances and the assay as rapidly as possible and protected from actinic light and air.

Related substances

A. Thin-layer chromatography (2.2.27).

Solution A To 1 mL of *triethylamine R* add 9 mL of *chloroform R*.

Test solution Dissolve 1 mg of the substance to be examined in 100 µL of solution A.

Reference solution (a) To 10 µL of the test solution add 990 µL of solution A.

Reference solution (b) To 250 µL of reference solution (a) add 750 µL of solution A.

Reference solution (c) To 100 µL of reference solution (a) add 900 µL of solution A.

Reference solution (d) Place 2 mg of the substance to be examined in a vial and dissolve in 200 µL of solution A. Close the vial and keep it in a water-bath at 60 °C for 2 h.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *2-methylpropanol R*, *methylene chloride R* (20:80 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Application 10 µL of the test solution and reference solutions (b), (c) and (d).

Development Over 2/3 of the plate.

Drying In air, then at 140 °C for 10 min.

Detection Spray the hot plate with an *alcoholic solution of sulfuric acid R*, dry at 140 °C for not more than 1 min and examine in ultraviolet light at 366 nm.

Relative retention With reference to calcipotriol (R_F = about 0.4): impurity G = about 0.4; impurity H = about 0.4; pre-calcipotriol = about 0.9; impurity A = about 1.2.

System suitability Reference solution (d):

— the chromatogram shows a secondary spot due to pre-calcipotriol.

Limits:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent);

— *impurities G, H*: any spot due to impurity G or H is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent for the sum);

— *unspecified impurities*: any other spot is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.1 per cent).

B. Liquid chromatography (*2.2.29*).

Solution A Dissolve 1.32 g of *ammonium phosphate R* in *water R* and dilute to 10.0 mL with the same solvent.

Solvent mixture Solution A, *water R*, *methanol R* (0.3:29.7:70 *V/V/V*).

Test solution (a) Dissolve 2 mg of the substance to be examined in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Test solution (b) Dissolve 2.00 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 1 mg of *calcipotriol for system suitability CRS* (containing impurities B, C and D) in the solvent mixture and dilute to 2.5 mL with the solvent mixture.

Reference solution (d) Dissolve 2.00 mg of *calcipotriol monohydrate CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase *water for chromatography R*, *methanol R* (30:70 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 264 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time Twice the retention time of calcipotriol.

Identification of impurities Use the chromatogram supplied with *calcipotriol for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, C and D.

Relative retention With reference to calcipotriol (retention time = about 13.5 min): impurity B = about 0.86; impurity C = about 0.92; impurity D = about 1.3.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to calcipotriol.

Limits:

— *impurity B*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying

Maximum 1.0 per cent, determined on 5 mg by thermogravimetry (*2.2.34*). Heat to 105 °C at a rate of 10 °C/min and maintain at 105 °C for 60 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

www.webofpharma.com

https://thuocngocanh.com/

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{27}H_{40}O_3$ taking into account the assigned content of *calcipotriol monohydrate CRS* and, if necessary, the peak due to pre-calcipotriol.

STORAGE

In an airtight container, protected from light, at -20 °C or below.

IMPURITIES

Test A for related substances

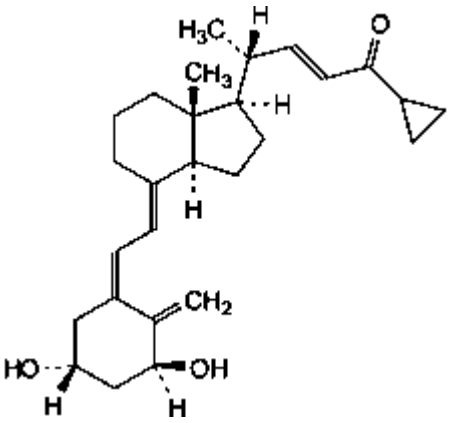
A, G, H, I.

Test B for related substances

B, C, D, E, F.

Specified impurities *A, B, C, D, G, H.*

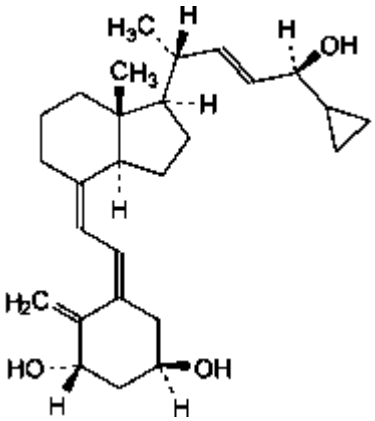
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, I.*



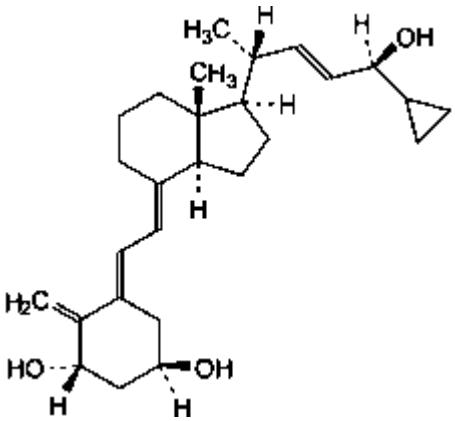
A. (5*Z*,7*E*,22*E*)-24-cyclopropyl-1α,3β-dihydroxy-9,10-secochola-5,7,10(19),22-tetraen-24-one,

www.webofpharma.com

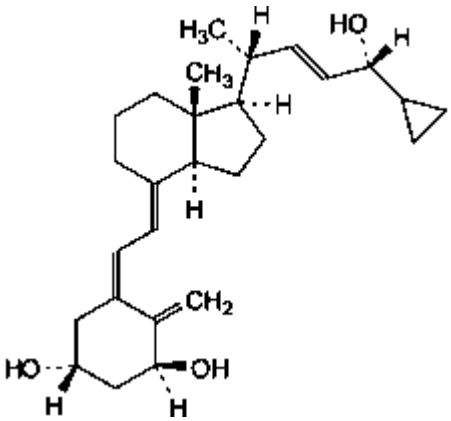
https://thuocngocanh.com/



B. (5*Z*,7*Z*,22*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol ((7*Z*)-calcipotriol),



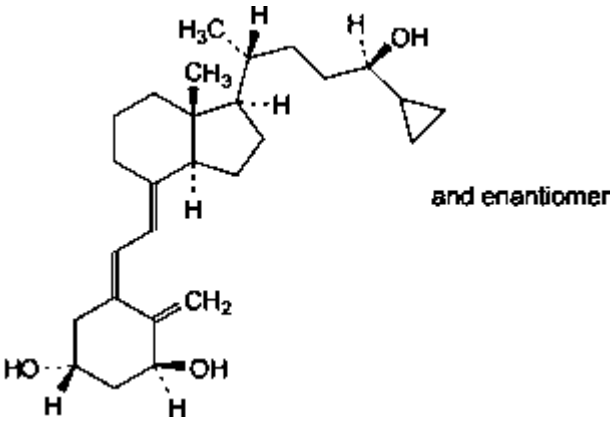
C. (5*E*,7*E*,22*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol ((5*E*)-calcipotriol),



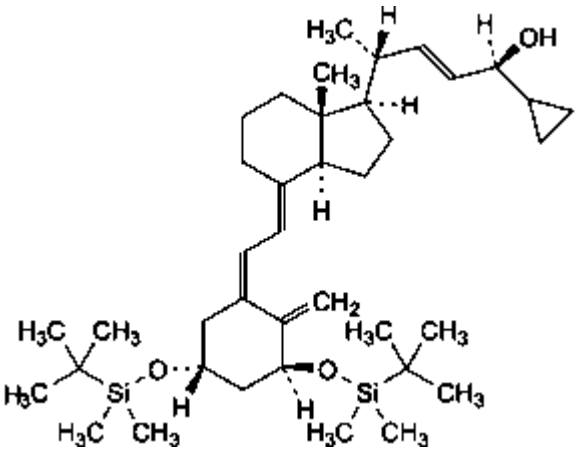
D. (5*Z*,7*E*,22*E*,24*R*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol (24-*epi*-calcipotriol),

www.webofpharma.com

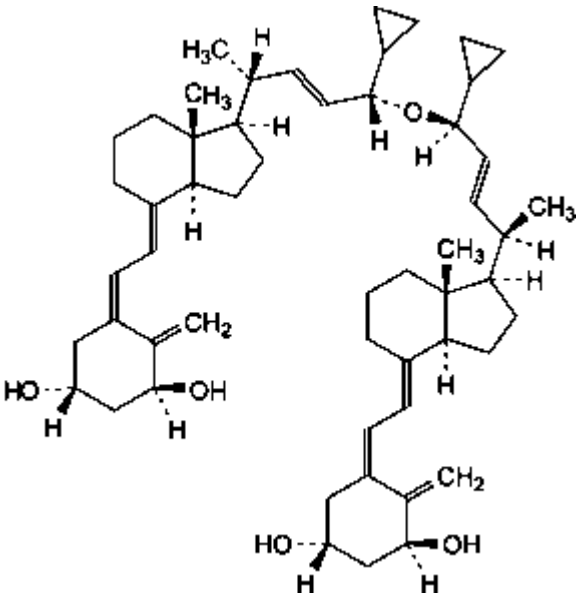
https://thuocngocanh.com/



E. *rac*-(5*Z*,7*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19)-triene-1α,3β,24-triol,



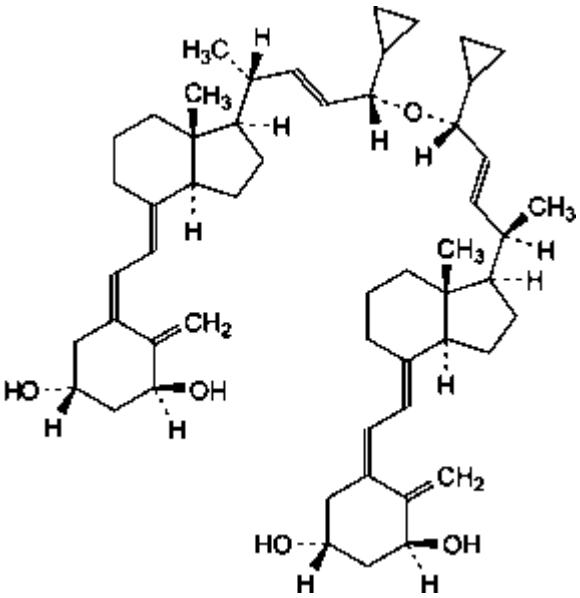
F. (5*Z*,7*E*,22*E*,24*S*)-24-cyclopropyl-1α,3β-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9,10-secochola-5,7,10(19),22-tetraen-24-ol,



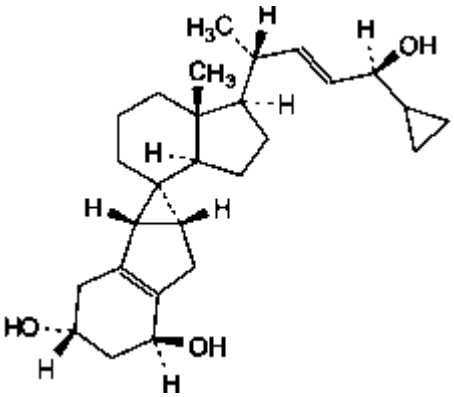
G. 24,24′-oxybis[(5*Z*,7*E*,22*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β-diol],

www.webofpharma.com

https://thuocngocanh.com/



H. (5*Z*,7*E*,22*E*,24*R*)-24-cyclopropyl-24-[[(5*Z*,7*E*,22*E*,24*S*)-24-cyclopropyl-1α,3β-dihydroxy-9,10-secochola-5,7,10(19),22-tetraen-24-yl]oxy]-9,10-secochola-5,7,10(19),22-tetraene-1α,3β-diol,



I. (6*S*,7*R*,8*R*,22*E*,24*S*)-24-cyclopropyl-6,8:7,19-dicyclo-9,10-secochola-5(10),22-diene-1α,3β,24-triol (suprasterol of calcipotriol).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcipotriol and Betamethasone Cutaneous Foam

General Notices

Action and use

Vitamin D analogue + glucocorticoid.

DEFINITION

Calcipotriol and Betamethasone Cutaneous Foam contains Calcipotriol Monohydrate and Betamethasone Dipropionate in a suitable basis.

The cutaneous foam complies with the requirements stated under Medicated Foams and with the following requirements.

Content of calcipotriol, $C_{27}H_{40}O_3$

92.0 to 105.0% of the stated amount.

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

Content of betamethasone, $C_{22}H_{29}FO_5$

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. *For calcipotriol* In the Assay, the *light absorption*, Appendix II B, of the peak due to calcipotriol in solution (1) in the range 220 to 360 nm is similar to the spectrum obtained with the principal peak in solution (2).

B. *For calcipotriol* In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

C. *For betamethasone* In the Assay, the *light absorption*, Appendix II B, of the peak due to betamethasone in solution (1) in the range 220 to 360 nm is similar to the spectrum obtained with the principal peak in solution (2).

D. *For betamethasone* In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (3) is similar to that of the peak in the chromatogram obtained with solution (4).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.132% w/v solution of *diammonium hydrogen orthophosphate* adjusted to pH 6.4 using 1M *orthophosphoric acid*

www.webofpharma.com

https://thuocngocanh.com/

Solution B 60 volumes of *acetonitrile* and 40 volumes of solution A.

(1) On a water bath, disperse a quantity of foam containing the equivalent of 0.9 mg of calcipotriol in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.

(2) On a water bath, melt a quantity of foam containing the equivalent of 90 mg of betamethasone in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.

(3) 0.00075% w/v of *calcipotriol EPCRS* and 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.

(4) 0.00075% w/v of *calcipotriol EPCRS* in mobile phase A.

(5) 0.097% w/v of *betamethasone dipropionate for system suitability A EPCRS* in mobile phase A.

(6) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A, and further dilute 1 volume to 20 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (150 mm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography (UHPLC)* (1.8 µm) (Zorbax Eclipse Plus RRHD is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.4 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a photodiode array (PDA) detector with a detection wavelength of 264 nm.

(f) Inject 15 µL of each solution.

MOBILE PHASE

Mobile phase A 40 volumes of *acetonitrile* and 60 volumes of solution A.

Mobile phase B 80 volumes of *acetonitrile* and 20 volumes of solution A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-38	100→10	0→90	linear gradient
38-39	10→0	90→100	linear gradient
39-43	0	100	isocratic
43-44	0→100	100→0	linear gradient
44-50	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retentions relative to calcipotriol (retention time, about 14 minutes) are about:

www.webofpharma.com

https://thuvienthuocngocanh.com/

RRT	Impurity	RRT	Impurity
0.91	Pre-calcipotriol	1.16	Betamethasone unknown*
0.96	Caclipotriol impurity C	1.19	Betamethasone unknown*
1.12	Caclipotriol impurity D	1.23	Betamethasone impurity E
0.42	Betamethasone impurity B	1.27	Betamethasone unknown*
0.52	Betamethasone unknown*	1.43	Betamethasone unknown*
0.54	Betamethasone impurity C	1.47	Betamethasone unknown*
0.84	Betamethasone impurity D	1.51	Betamethasone unknown*
1.05	Betamethasone unknown*	1.58	Betamethasone unknown*

* UV scan from a PDA detector, or response ratios from a dual wavelength detector, should be used in conjunction with the information above to attribute unknown peaks to the relevant active ingredient.

*Where Betamethasone impurities are indicated, these relate to Betamethasone dipropionate impurities.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley* ratio is at least 1.5, where H_p is the height above the baseline of the peak due to calcipotriol impurity D and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate.

LIMITS

Identify any secondary peaks and attribute to the correct API using solutions (4) and (5) and the information included in the above table.

For calcipotriol

Calculate the results by *normalisation*, using all peaks attributed to calcipotriol. Any secondary peak that cannot be attributed to an impurity of betamethasone dipropionate should be calculated with respect to calcipotriol.

In the chromatogram obtained with solution (1):

the area of any peak due to calcipotriol impurity C is not more than 1.5%;

the area of any peak due to calcipotriol impurity D is not more than 1%.

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of all secondary peaks is not greater than 1.5%.

Disregard any peak with an area less than 0.1% and any peak due to betamethasone dipropionate or related impurities.

For betamethasone dipropionate

www.webofpharma.com

https://thuocngocanh.com/

Calculate the results by *normalisation*, using all peaks attributed to betamethasone dipropionate.

In the chromatogram obtained with solution (2):

the area of any peak due to betamethasone impurity B is not more than 0.8%;

the area of any peak due to betamethasone impurity C is not more than 0.8%;

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of all secondary peaks, excluding impurities B and C, is not greater than 1%.

Disregard any peak with an area less than 0.1% and any peak attributed to calcipotriol and pre-calcipotriol or related impurities.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.132% w/v solution of *diammonium hydrogen orthophosphate* adjusted to pH 6.4 using 1M *orthophosphoric acid*.

Solution B 40 volumes of solution A and 60 volumes of *acetonitrile*.

(1) On a *water bath*, melt a quantity of cutaneous foam containing the equivalent of 0.9 mg of calcipotriol in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(2) 0.00075% w/v of *calcipotriol EPCRS* in mobile phase A.
(3) On a *water bath,* melt a quantity of cutaneous foam containing the equivalent of 90 mg of betamethasone in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(4) 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.
(5) 0.00075% w/v of *calcipotriol EPCRS* and 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley* ratio is at least 1.5, where H_p is the height above the baseline of the peak due to calcipotriol impurity D and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate.

DETERMINATION OF CONTENT

For calcipotriol

Combine the peaks due to calcipotriol and pre-calcipotriol. Calculate the content of $C_{27}H_{40}O_3$ in the cutaneous foam using the declared content of $C_{27}H_{40}O_3$ in *calcipotriol EPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

For betamethasone

Calculate the content of betamethasone ($C_{22}H_{29}FO_5$) in the cutaneous foam using the declared content of betamethasone dipropionate ($C_{28}H_{37}FO_7$) in betamethasone dipropionate EPCRS. Each mg of $C_{28}H_{37}FO_7$ is equivalent to 0.7778 mg of $C_{22}H_{29}FO_5$.

LABELLING

The quantity of active ingredients are stated in terms of the equivalent amount of calcipotriol and the equivalent amount of betamethasone.

IMPURITIES

The impurities limited by the requirements of this monograph include the following impurities stated under Calcipotriol Monohydrate and Betamethasone Dipropionate:

calcipotriol impurity C

calcipotriol impurity D

betamethasone dipropionate impurity B

betamethasone dipropionate impurity C

betamethasone dipropionate impurity D

betamethasone dipropionate impurity E

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcipotriol and Betamethasone Gel

General Notices

Action and use

Vitamin D analogue + glucocorticoid.

DEFINITION

Calcipotriol and Betamethasone Gel contains Calcipotriol Monohydrate and Betamethasone Dipropionate in a suitable basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of calcipotriol, $C_{27}H_{40}O_3$

92.0 to 105.0% of the stated amount.

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

Content of betamethasone, $C_{22}H_{29}FO_5$

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. *For calcipotriol* In the Assay, the *light absorption*, Appendix II B, of the peak due to calcipotriol in solution (1) in the range 220 to 360 nm is similar to the spectrum obtained with solution (2).

B. *For calcipotriol* In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

C. *For betamethasone* In the Assay, the *light absorption*, Appendix II B, of the peak due to betamethasone in solution (1) in the range 220 to 360 nm is similar to the spectrum obtained with the principal peak in solution (2).

D. *For betamethasone* In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (3) is similar to that of the peak in the chromatogram obtained with solution (4).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.132% w/v solution of *diammonium hydrogen orthophosphate* adjusted to pH 6.4 using 1M *orthophosphoric acid*

www.webofpharma.com

https://thuocngocanh.com/

Solution B 60 volumes of *acetonitrile* and 40 volumes of solution A.

(1) On a water bath, disperse a quantity of gel containing the equivalent of 0.9 mg of betamethasone in 10 mL of *n-heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.

(2) On a water bath, melt a quantity of gel containing the equivalent of 90 mg of betamethasone in 10 mL of *n-heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.

(3) 0.00075% w/v of *calcipotriol EPCRS* and 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.

(4) 0.00075% w/v of *calcipotriol EPCRS* in mobile phase A.

(5) 0.097% w/v of *betamethasone dipropionate for system suitability A EPCRS* in mobile phase A.

(6) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A, and further dilute 1 volume to 20 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (150 mm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography (UHPLC)* (1.8 µm) (Zorbax Eclipse Plus RRHD is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.4 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a photodiode array (PDA) detector with a detection wavelength of 264 nm.

(f) Inject 15 µL of each solution.

MOBILE PHASE

Mobile phase A 40 volumes of *acetonitrile* and 60 volumes of solution A.

Mobile phase B 80 volumes of *acetonitrile* and 20 volumes of solution A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-38	100→10	0→90	linear gradient
38-39	10→0	90→100	linear gradient
39-43	0	100	isocratic
43-44	0→100	100→0	linear gradient
44-50	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retentions relative to calcipotriol (retention time, about 14 minutes) are about:

www.webofpharma.com

https://thietbiuocngocanh.com/

RRT	Impurity	RRT	Impurity
0.91	Pre-calcipotriol	1.16	Betamethasone unknown*
0.96	Caclipotriol impurity C	1.19	Betamethasone unknown*
1.12	Caclipotriol impurity D	1.23	Betamethasone impurity E
0.42	Betamethasone impurity B	1.27	Betamethasone unknown*
0.52	Betamethasone unknown*	1.43	Betamethasone unknown*
0.54	Betamethasone impurity C	1.47	Betamethasone unknown*
0.84	Betamethasone impurity D	1.51	Betamethasone unknown*
1.05	Betamethasone unknown*	1.58	Betamethasone unknown*

* UV scan from a PDA detector, or response ratios from a dual wavelength detector, should be used in conjunction with the information above to attribute unknown peaks to the relevant active ingredient.

*Where Betamethasone impurities are indicated, these relate to Betamethasone dipropionate impurities.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the peak-to-valley ratio is at least 1.5, where H_p is the height above the baseline of the peak due to calcipotriol impurity D and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate.

LIMITS

Identify any secondary peaks and attribute to the correct API using solutions (4) and (5) and the information included in the above table.

For calcipotriol

Calculate the results by *normalisation*, using all peaks attributed to calcipotriol. Any secondary peak that cannot be attributed to an impurity of betamethasone dipropionate should be calculated with respect to calcipotriol.

In the chromatogram obtained with solution (1):

the area of any peak due to calcipotriol impurity C is not more than 1.5%;

the area of any peak due to calcipotriol impurity D is not more than 1%.

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of all secondary peaks is not greater than 1.5%.

Disregard any peak with an area less than 0.05% and any peak due to betamethasone dipropionate.

For betamethasone dipropionate

www.webofpharma.com

https://thuocngocanh.com/

Calculate the results by *normalisation*, using all peaks attributed to betamethasone dipropionate.

In the chromatogram obtained with solution (2):

the area of any peak due to betamethasone impurity B is not more than 0.8%;

the area of any peak due to betamethasone impurity C is not more than 0.8%;

the area of any other *secondary peak* is not greater than 0.50%;

the sum of the areas of all *secondary peaks*, excluding impurities B and C, is not greater than 1.0%.

Disregard any peak with an area less than 0.1% and any peak attributed to calcipotriol and pre-calcipotriol or related impurities.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.132% w/v solution of *diammonium hydrogen orthophosphate* adjusted to pH 6.4 using 1M *orthophosphoric acid*

Solution B 40 volumes of solution A and 60 volumes of *acetonitrile*.

(1) On a water bath, melt a quantity of gel containing the equivalent of 0.9 mg of calcipotriol in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(2) 0.00075% w/v of *calcipotriol EPCRS* in mobile phase A.
(3) On a water batch melt a quantity of gel containing the equivalent of 90 mg of betamethasone in 10 mL of n-*heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(4) 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.
(5) 0.00075% w/v of *calcipotriol EPCRS* and 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 1.5, where H_p is the height above the baseline of the peak due to calcipotriol impurity D and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate.

DETERMINATION OF CONTENT

For calcipotriol

Combine the areas of the peaks due to calcipotriol and pre-calcipotriol. Calculate the content of $C_{27}H_{40}O_3$ in the gel using the declared content of $C_{27}H_{40}O_3$ in *calcipotriol EPCRS*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

For betamethasone

Calculate the content of betamethasone ($C_{22}H_{29}FO_5$) in the gel using the declared content of betamethasone dipropionate ($C_{28}H_{37}FO_7$) in betamethasone dipropionate EPCRS. Each mg of $C_{28}H_{37}FO_7$ is equivalent to 0.7778 mg of $C_{22}H_{29}FO_5$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of calcipotriol and the equivalent amount of betamethasone.

IMPURITIES

The impurities limited by the requirements of this monograph include the following impurities stated under Calcipotriol Monohydrate and Betamethasone Dipropionate:

calcipotriol impurity C

calcipotriol impurity D

betamethasone dipropionate impurity B

betamethasone dipropionate impurity C

betamethasone dipropionate impurity D

betamethasone dipropionate impurity E

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcipotriol and Betamethasone Ointment

General Notices

Action and use

Vitamin D analogue + glucocorticoid.

DEFINITION

Calcipotriol and Betamethasone Ointment contains Calcipotriol Monohydrate and Betamethasone Dipropionate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of calcipotriol, $C_{27}H_{40}O_3$

92.0 to 105.0% of the stated amount.

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

Content of betamethasone, $C_{22}H_{29}FO_5$

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. *For calcipotriol* In the Assay, the *light absorption*, Appendix II B, of the peak due to calcipotriol in solution (1) in the range 220 to 360 nm is similar to the spectrum obtained with the principal peak in solution (2).

B. *For calcipotriol* In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

C. *For betamethasone* In the Assay, the *light absorption*, Appendix II B, of the peak due to betamethasone in solution (1) in the range 220 to 360 nm is similar to the spectrum obtained with the principal peak in solution (2).

D. *For betamethasone* In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (3) is similar to that of the peak in the chromatogram obtained with solution (4).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.132% w/v solution of *diammonium hydrogen orthophosphate* adjusted to pH 6.4 using 1M *orthophosphoric acid*

www.webofpharma.com

https://thuocngocanh.com/

Solution B 60 volumes of *acetonitrile* and 40 volumes of solution A.

(1) On a *water bath*, disperse a quantity of ointment containing the equivalent of 0.9 mg of calciprotriol in 10 mL of *n-heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.

(2) On a *water bath*, melt a quantity of ointment containing the equivalent of 90 mg of betamethasone in 10 mL of *n-heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.

(3) 0.00075% w/v of *calcipotriol EPCRS* and 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.

(4) 0.00075% w/v of *calcipotriol EPCRS* in mobile phase A.

(5) 0.097% w/v of *betamethasone dipropionate for system suitability A EPCRS* in mobile phase A.

(6) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A, and further dilute 1 volume to 20 volumes with the same solvent.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (150 mm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography (UHPLC)* (1.8 µm) (Zorbax Eclipse Plus RRHD is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.4 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a photodiode array (PDA) detector with a detection wavelength of 264 nm.

(f) Inject 15 µL of each solution.

MOBILE PHASE

Mobile phase A 40 volumes of *acetonitrile* and 60 volumes of solution A.

Mobile phase B 80 volumes of *acetonitrile* and 20 volumes of solution A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-38	100→10	0→90	linear gradient
38-39	10→0	90→100	linear gradient
39-43	0	100	isocratic
43-44	0→100	100→0	linear gradient
44-50	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retentions relative to calcipotriol (retention time, about 14 minutes) are about:

RRT	Impurity	RRT	Impurity
0.91	Pre-calcipotriol	1.16	Betamethasone unknown*

www.webofpharma.com

https://thietbiuocngocanh.com/

RRT	Impurity	RRT	Impurity
0.96	Caclipotriol impurity C	1.19	Betamethasone unknown*
1.12	Caclipotriol impurity D	1.23	Betamethasone impurity E*
0.42	Betamethasone impurity B	1.27	Betamethasone unknown*
0.52	Betamethasone unknown*	1.43	Betamethasone unknown*
0.54	Betamethasone impurity C*	1.47	Betamethasone unknown*
0.84	Betamethasone impurity D*	1.51	Betamethasone unknown*
1.05	Betamethasone unknown*	1.58	Betamethasone unknown*

* UV scan from a PDA detector, or response ratios from a dual wavelength detector, should be used in conjunction with the information above to attribute unknown peaks to the relevant active ingredient.

*Where Betamethasone impurities are indicated, these relate to Betamethasone dipropionate impurities.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the peak-to-valley ratio is at least 1.5, where H_p is the height above the baseline of the peak due to calcipotriol impurity D, and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate.

LIMITS

Identify any secondary peaks and attribute to either calcipotriol or betamethasone, using solutions (4) and (5) and the information included in the above table.

For calcipotriol

Calculate the results by *normalisation*, using all peaks attributed to calcipotriol. Any secondary peak that cannot be attributed to an impurity of betamethasone dipropionate should be calculated with respect to calcipotriol.

In the chromatogram obtained with solution (1):

the area of any peak due to calcipotriol impurity C is not more than 1.5%;

the area of any peak due to calcipotriol impurity D is not more than 1%.

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of all *secondary peaks* is not greater than 1.5%.

Disregard any peak less than 0.05% and any peak due to betamethasone dipropionate.

For betamethasone dipropionate

Calculate the results by *normalisation*, using all peaks attributed to betamethasone dipropionate.

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (2):

the area of any peak due to betamethasone impurity B is not more than 0.8%;

the area of any peak due to betamethasone impurity C is not more than 0.8%;

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of all *secondary peaks*, excluding impurities B and C, is not greater than 1.0%.

Disregard any peak with an area less than 0.1% and any peak attributed to calcipotriol and pre-calcipotriol or related impurities.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.132% w/v solution of *diammonium hydrogen orthophosphate* adjusted to pH 6.4 using 1M *orthophosphoric acid*

Solution B 40 volumes of solution A and 60 volumes of *acetonitrile*.

(1) On a *water bath*, melt a quantity of ointment containing the equivalent of 0.9 mg of calcipotriol in 10 mL of *n-heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(2) 0.00075% w/v of *calcipotriol EPCRS* in mobile phase A.
(3) On a *water bath,* melt a quantity of ointment containing the equivalent of 90 mg of betamethasone in 10 mL of *n-heptane*. Add 8 mL of solution B and shake for 15 minutes. Allow to separate and add 4 mL of the lower (aqueous) layer to 2 mL of solution A, centrifuge and use the clear lower layer.
(4) 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.
(5) 0.00075% w/v of *calcipotriol EPCRS* and 0.097% w/v of *betamethasone dipropionate EPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 1.5, where H_p is the height above the baseline of the peak due to calcipotriol impurity D and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to betamethasone dipropionate.

DETERMINATION OF CONTENT

For calcipotriol

Combine the areas of the peaks due to calcipotriol and pre-calcipotriol. Calculate the content of $C_{27}H_{40}O_3$ in the ointment using the declared content of $C_{27}H_{40}O_3$ in *calcipotriol EPCRS*.

For betamethasone

www.webofpharma.com

https://thietbiuocngocanh.com/

Calculate the content of betamethasone ($C_{22}H_{29}FO_5$) in the ointment using the declared content of betamethasone dipropionate ($C_{28}H_{37}FO_7$) in betamethasone dipropionate EPCRS. Each mg of $C_{28}H_{37}FO_7$ is equivalent to 0.7778 mg of $C_{22}H_{29}FO_5$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of calcipotriol and the equivalent amount of betamethasone.

IMPURITIES

The impurities limited by the requirements of this monograph include the following impurities stated under Calcipotriol Monohydrate and Betamethasone Dipropionate:

calcipotriol impurity C

calcipotriol impurity D

betamethasone dipropionate impurity B

betamethasone dipropionate impurity C

betamethasone dipropionate impurity D

betamethasone dipropionate impurity E

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcipotriol Cream

General Notices

Action and use

Vitamin D analogue.

DEFINITION

Calcipotriol Cream contains either Calcipotriol or Calcipotriol Monohydrate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of calcipotriol, $C_{27}H_{40}O_3$

95.0 to 105.0% of the stated amount.

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

Solvent A 1 volume of *triethylamine* and 9 volumes of *dichloromethane*.

(1) To a quantity of the cream containing the equivalent of 0.5 mg of calcipotriol, add 50 mL of *absolute ethanol* and shake vigorously. Cool in ice and filter. Evaporate the filtrate to dryness at a temperature not exceeding 30° and dissolve the residue in 1 mL of solvent A.
(2) 0.05% w/v of *calcipotriol monohydrate EPCRS* in solvent A.
(3) Place 2 mg of *calcipotriol monohydrate EPCRS* in a vial and dissolve in 200 µL of solvent A. Close the vial and keep it in a water bath at 60° for 2 hours (generation of pre-calcipotriol).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.
(b) Use the mobile phase as described below.
(c) Apply 50 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and then heat at 140° for 10 minutes. Whilst hot, spray the plate with an *alcoholic solution of sulfuric acid*, dry at 140° for not more than 1 minute and examine in *ultraviolet light (366 nm)*.

MOBILE PHASE

20 volumes of *2-methylpropanol* and 80 volumes of *dichloromethane*.

www.webofpharma.com

https://thietbiuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2). A secondary spot in the chromatogram obtained with solution (1) corresponds in position and colour to the pre-calcipotriol spot in solution (3).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to calcipotriol in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared in solvent B.

Solvent B 30 volumes of 0.01M *ammonium phosphate* and 70 volumes of *methanol*.

(1) To a quantity of the cream containing the equivalent of 0.5 mg of calcipotriol, add 10 mL of *methanol* and shake vigorously. Cool in ice, centrifuge and filter. Evaporate 5 mL of the filtrate to dryness at a temperature not exceeding 30° and dissolve the residue in 2 mL of solvent B.

(2) Dilute 0.1 mL of solution (1) to 10 mL.

(3) 0.004% w/v of *calcipotriol monohydrate EPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Luna C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 264 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 2 times the retention time of calcipotriol.

MOBILE PHASE

30 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to calcipotriol (retention time, about 13.5 minutes) are: pre-calcipotriol, about 0.86; impurity C, about 0.92 and impurity D, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* between calcipotriol and impurity C is at least 5.

www.webofpharma.com

https://thietbiuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) To a quantity of the cream containing the equivalent of 0.25 mg of calcipotriol, add 7 mL of *methanol* and shake vigorously. Dilute to 20 mL with 0.01M *ammonium phosphate*. Cool in ice, centrifuge and filter.
(2) 0.0013% w/v of *calcipotriol monohydrate EPCRS* in solvent B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with an injection volume of 200 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *peak-to-valley ratio* between calcipotriol and impurity C is at least 5.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{40}O_3$ in the cream using the combined areas of the peaks due to calcipotriol and pre-calcipotriol in the chromatograms obtained with solutions (1) and (2) and the declared content of $C_{27}H_{40}O_3$ in *calcipotriol monohydrate EPCRS*.

STORAGE

Calcipotriol Cream should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of calcipotriol.

www.webofpharma.com

https://thietbiuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

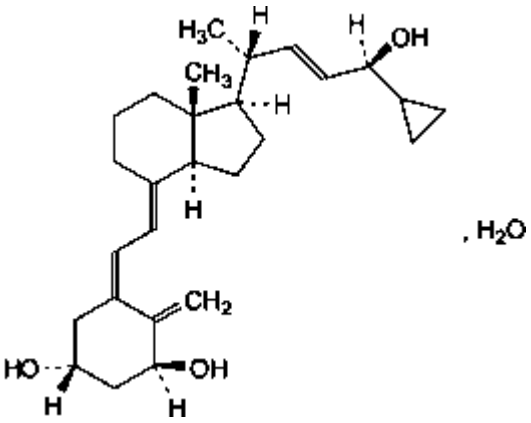
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcipotriol Monohydrate

General Notices

(Ph. Eur. monograph 2284)



$C_{27}H_{40}O_3,H_2O$ 430.6 *147657-22-5*

Action and use

Vitamin D analogue.

Preparations

Calcipotriol Cream

Calcipotriol Ointment

Calcipotriol Scalp Application

Ph Eur

DEFINITION

(5*Z*,7*E*,22*E*,24*S*)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol monohydrate.

Content

95.5 per cent to 102.0 per cent (anhydrous substance).

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

It is sensitive to light.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of calcipotriol monohydrate*.

B. Water (see Tests).

TESTS

Carry out the tests for related substances and the assay as rapidly as possible and protected from actinic light and air.

Related substances

A. Thin-layer chromatography (2.2.27).

Solution A To 1 mL of *triethylamine R* add 9 mL of *chloroform R*.

Test solution Dissolve 1 mg of the substance to be examined in 100 µL of solution A.

Reference solution (a) To 10 µL of the test solution add 990 µL of solution A.

Reference solution (b) To 250 µL of reference solution (a) add 750 µL of solution A.

Reference solution (c) To 100 µL of reference solution (a) add 900 µL of solution A.

Reference solution (d) Place 2 mg of the substance to be examined in a vial and dissolve in 200 µL of solution A. Close the vial and keep it in a water bath at 60 °C for 2 h.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *2-methylpropanol R*, *methylene chloride R* (20:80 *V/V*).

Application 10 µL of the test solution and reference solutions (b), (c) and (d).

Development Over 2/3 of the plate.

Drying In air, then at 140 °C for 10 min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spray the hot plate with an *alcoholic solution of sulfuric acid R*, dry at 140 °C for not more than 1 min and examine in ultraviolet light at 366 nm.

Relative retention With reference to calcipotriol (R_F = about 0.4): impurity G = about 0.4; impurity H = about 0.4; pre-calcipotriol = about 0.9; impurity A = about 1.2.

System suitability Reference solution (d):

— the chromatogram shows a secondary spot due to pre-calcipotriol.

Limits:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent);

— *impurities G, H*: any spot due to impurity G or H is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent for the sum);

— *unspecified impurities*: any other spot is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.1 per cent).

B. Liquid chromatography (*2.2.29*).

Solution A Dissolve 1.32 g of *ammonium phosphate R* in *water R* and dilute to 10.0 mL with the same solvent.

Solvent mixture Solution A, *water R*, *methanol R* (0.3:29.7:70 *V/V/V*).

Test solution (a) Dissolve 2 mg of the substance to be examined in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Test solution (b) Dissolve 2.00 mg of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 1 mg of *calcipotriol for system suitability CRS* (containing impurities B, C and D) in the solvent mixture and dilute to 2.5 mL with the solvent mixture.

Reference solution (d) Dissolve 2.00 mg of *calcipotriol monohydrate CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase *water for chromatography R*, *methanol R* (30:70 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 264 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time Twice the retention time of calcipotriol.

Identification of impurities Use the chromatogram supplied with *calcipotriol for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, C and D.

Relative retention With reference to calcipotriol (retention time = about 13.5 min): impurity B = about 0.86; impurity C = about 0.92; impurity D = about 1.3.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to calcipotriol.

Limits:

— *impurity B*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

3.3 per cent to 5.0 per cent, determined on 0.100 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{27}H_{40}O_3$ taking into account the assigned content of *calcipotriol monohydrate CRS* and, if necessary, the peak due to pre-calcipotriol.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

In an airtight container, protected from light.

IMPURITIES

Test A for related substances

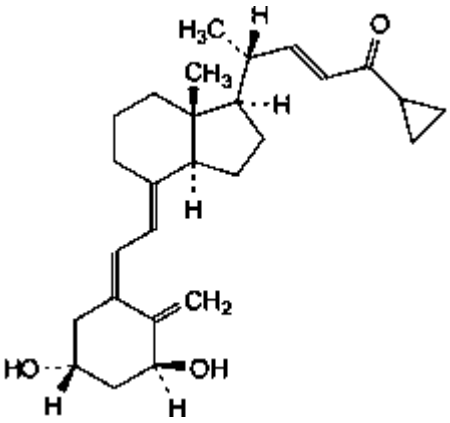
A, G, H, I.

Test B for related substances

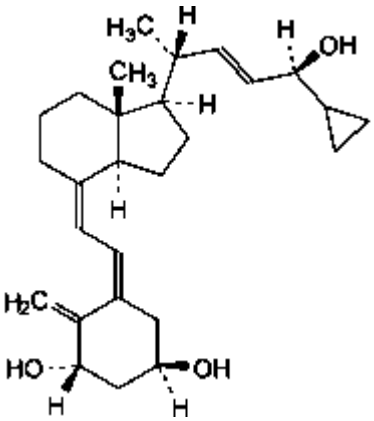
B, C, D, E, F.

Specified impurities *A, B, C, D, G, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, I.*



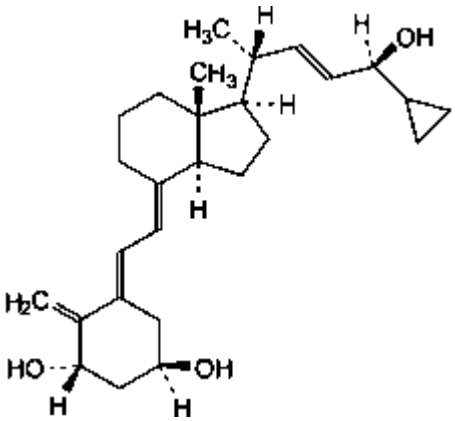
A. (5*Z*,7*E*,22*E*)-24-cyclopropyl-1α,3β-dihydroxy-9,10-secochola-5,7,10(19),22-tetraen-24-one,



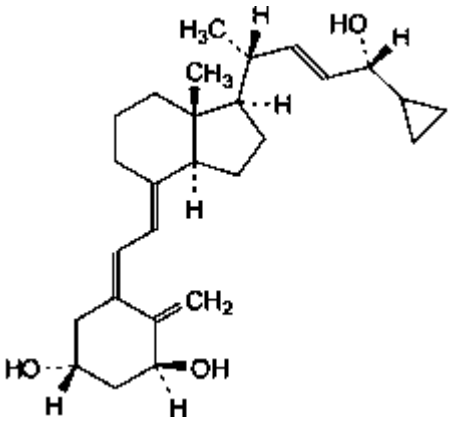
B. (5*Z*,7*Z*,22*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol ((7*Z*)-calcipotriol),

www.webofpharma.com

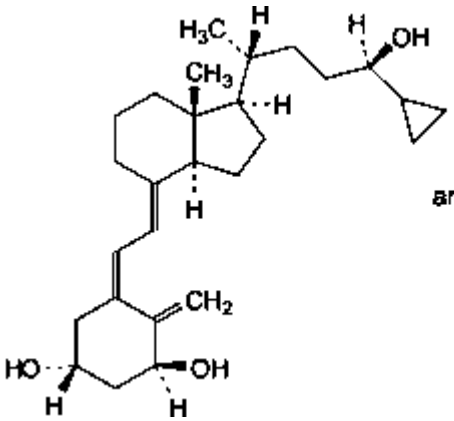
https://thuocngocanh.com/



C. (5*E*,7*E*,22*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol ((5*E*)-calcipotriol),



D. (5*Z*,7*E*,22*E*,24*R*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol (24-*epi*-calcipotriol),

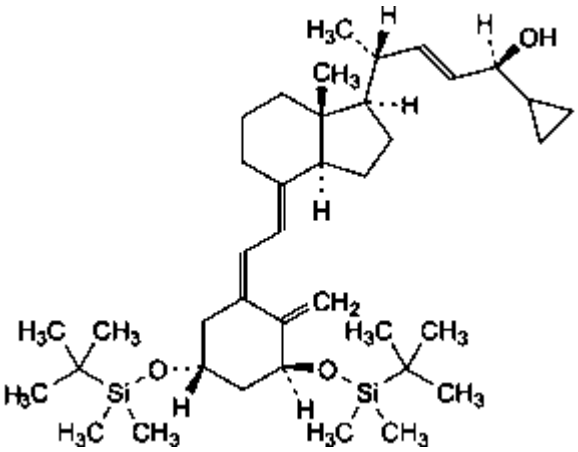


and enantiomer

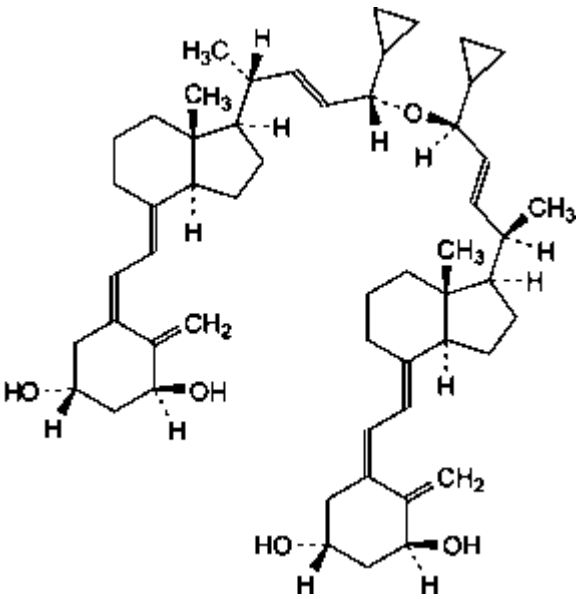
E. *rac*-(5*Z*,7*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19)-triene-1α,3β,24-triol,

www.webofpharma.com

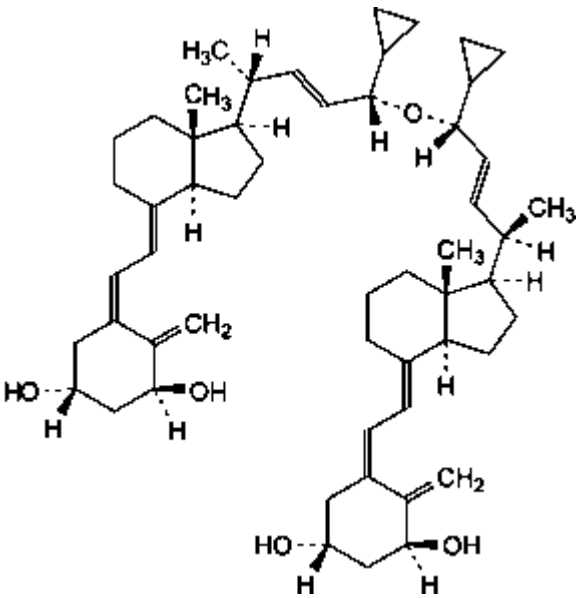
https://thuocngocanh.com/



F. (5*Z*,7*E*,22*E*,24*S*)-24-cyclopropyl-1α,3β-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9,10-secochola-5,7,10(19),22-tetraen-24-ol,



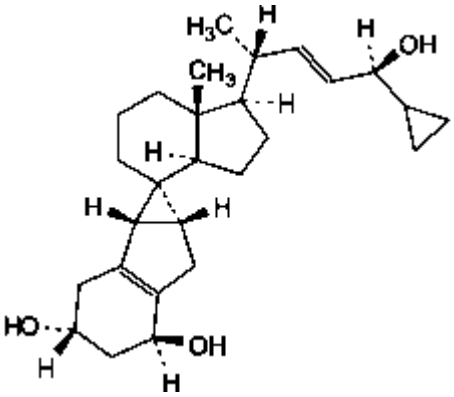
G. 24,24′-oxybis[(5*Z*,7*E*,22*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β-diol],



www.webofpharma.com

https://thuocngocanh.com/

H. (5*Z*,7*E*,22*E*,24*R*)-24-cyclopropyl-24-[[(5*Z*,7*E*,22*E*,24*S*)-24-cyclopropyl-1α,3β-dihydroxy-9,10-secochola-5,7,10(19),22-tetraen-24-yl]oxy]-9,10-secochola-5,7,10(19),22-tetraene-1α,3β-diol,



I. (6*S*,7*R*,8*R*,22*E*,24*S*)-24-cyclopropyl-6,8:7,19-dicyclo-9,10-secochola-5(10),22-diene-1α,3β,24-triol (suprasterol of calcipotriol).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcipotriol Ointment

General Notices

Action and use

Vitamin D analogue.

DEFINITION

Calcipotriol Ointment contains either Calcipotriol or Calcipotriol Monohydrate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of calcipotriol, $C_{27}H_{40}O_3$

95.0 to 105.0% of the stated amount.

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

Solvent A

1 volume of *triethylamine* and 9 volumes of *dichloromethane*.

(1) To a quantity of the ointment containing the equivalent of 0.5 mg of calcipotriol, add 50 mL of *absolute ethanol* and shake vigorously. Cool in ice and filter. Evaporate the filtrate to dryness at a temperature not exceeding 30° and dissolve the residue in 1 mL of solvent A.

(2) 0.05% w/v of *calcipotriol monohydrate EPCRS* in solvent A.

(3) Place 2 mg of *calcipotriol monohydrate EPCRS* in a vial and dissolve in 200 µL of solvent A. Close the vial and keep it in a water bath at 60° for 2 hours (generation of pre-calcipotriol).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and then heat at 140° for 10 minutes. Whilst hot, spray the plate with an *alcoholic solution of sulfuric acid*, dry at 140° for not more than 1 minute and examine in *ultraviolet light (365 nm)*.

MOBILE PHASE

www.webofpharma.com

https://thietbiuocngocanh.com/

20 volumes of *2-methylpropanol* and 80 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2). A secondary spot in the chromatogram obtained with solution (1) corresponds in position and colour to the pre-calcipotriol spot in solution (3).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to calcipotriol in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared in solvent B.

Solvent B 30 volumes of 0.01M *ammonium phosphate* and 70 volumes of *methanol*.

(1) To a quantity of the ointment containing the equivalent of 0.5 mg of calcipotriol, add 10 mL of *methanol* and shake vigorously. Cool in ice, centrifuge and filter. Evaporate 5 mL of the filtrate to dryness at a temperature not exceeding 30° and dissolve the residue in 2 mL.
(2) Dilute 0.1 mL of solution (1) to 10 mL.
(3) 0.004% w/v of *calcipotriol monohydrate EPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Luna C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 264 nm.
(f) Inject 50 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 2 times the retention time of calcipotriol.

MOBILE PHASE

30 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to calcipotriol (retention time, about 13.5 minutes) are: impurity B, about 0.86; impurity C, about 0.92 and impurity D, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* between calcipotriol and impurity C is at least 5.

www.webofpharma.com

https://thietbiuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions.

(1) To a quantity of the ointment containing the equivalent of 0.25 mg of calcipotriol, add 7 mL of *methanol* and shake vigorously. Dilute to 20 mL with 0.01M *ammonium phosphate*. Cool in ice, centrifuge and filter.
(2) 0.0013% w/v of *calcipotriol monohydrate EPCRS* in solvent B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with an injection volume of 200 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *peak-to-valley ratio* between calcipotriol and impurity C is at least 5.

DETERMINATION OF CONTENT

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

Calculate the content of $C_{27}H_{40}O_3$ in the ointment using the chromatograms obtained with solutions (1) and (2) and the declared content of $C_{27}H_{40}O_3$ in *calcipotriol monohydrate EPCRS*.

STORAGE

Calcipotriol Ointment should be protected from light.

LABELLING

www.webofpharma.com

https://thietbiluocngocanh.com/

The quantity of active ingredient is stated in terms of the equivalent amount of calcipotriol.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcipotriol Scalp Application

General Notices

Action and use

Vitamin D analogue.

DEFINITION

Calcipotriol Scalp Application contains either Calcipotriol or Calcipotriol Monohydrate in a suitable basis.

The scalp application complies with the requirements stated under Liquids For Cutaneous Application and with the following requirements.

Content of calcipotriol, $C_{27}H_{40}O_3$

90.0 to 110.0% of the stated amount.

A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light, using the following solutions.

Solvent A

1 volume of *triethylamine* and 9 volumes of *dichloromethane*.

(1) Evaporate a quantity of the scalp application containing the equivalent of 0.5 mg of calcipotriol to dryness at a temperature not exceeding 30° and dissolve the residue in 1 mL of solvent A.

(2) 0.05% w/v of *calcipotriol monohydrate EPCRS* in solvent A.

(3) Place 2 mg of *calcipotriol monohydrate EPCRS* in a vial and dissolve in 200 µL of solvent A. Close the vial and keep it in a water bath at 60° for 2 hours (generation of pre-calcipotriol).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and then heat at 140° for 10 minutes. Whilst hot, spray the plate with an *alcoholic solution of sulfuric acid*, dry at 140° for not more than 1 minute and examine in *ultraviolet light (365 nm)*.

MOBILE PHASE

www.webofpharma.com

https://thietbiuocngocanh.com/

20 volumes of *2-methylpropanol* and 80 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2). A secondary spot in the chromatogram obtained with solution (1) corresponds in position and colour to the pre-calcipotriol spot in solution (3).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to calcipotriol in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared in solvent B.

Solvent B 30 volumes of 0.01M *ammonium phosphate* and 70 volumes of *methanol*.

(1) Evaporate a quantity of the scalp application containing the equivalent of 0.5 mg of calcipotriol to dryness at a temperature not exceeding 30° and dissolve the residue in 4 mL.
(2) Dilute 0.1 mL of solution (1) to 10 mL.
(3) 0.004% w/v of *calcipotriol monohydrate EPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Luna C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 264 nm.
(f) Inject 50 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for 2 times the retention time of calcipotriol.

MOBILE PHASE

30 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to calcipotriol (retention time, about 13.5 minutes) are: pre-calcipotriol, about 0.86; impurity C, about 0.92 and impurity D, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* between calcipotriol and impurity C is at least 5.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity D is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, protected from light, using the following solutions prepared in solvent B, as described under Related substances.

(1) Dilute a weight of the scalp application containing the equivalent of 0.35 mg of calcipotriol to 10 mL.
(2) 0.0037% w/v of *calcipotriol monohydrate EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *peak-to-valley ratio* between calcipotriol and impurity C is at least 5.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{40}O_3$ in the scalp application using the combined areas of the peaks due to calcipotriol and pre-calcipotriol in the chromatograms obtained with solutions (1) and (2) and the declared content of $C_{27}H_{40}O_3$ in *calcipotriol monohydrate EPCRS*.

STORAGE

Calcipotriol Scalp Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of calcipotriol.

www.webofpharma.com

https://thietbiuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

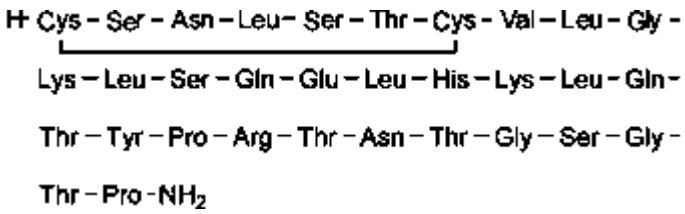
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcitonin (Salmon)

General Notices

(Ph. Eur. monograph 0471)



$C_{145}H_{240}N_{44}O_{48}S_2$ 3432

Action and use

Hormone.

Preparation

Calcitonin (Salmon) Injection

Ph Eur

DEFINITION

Polypeptide having the structure determined for salmon calcitonin I. It lowers the calcium concentration in plasma of mammals by diminishing the rate of bone resorption. It is obtained by chemical synthesis or by a method based on recombinant DNA (rDNA) technology. It is available as an acetate.

Content

90.0 per cent to 105.0 per cent of the peptide $C_{145}H_{240}N_{44}O_{48}S_2$ (anhydrous and acetic acid-free substance).

By convention, for the purpose of labelling calcitonin (salmon) preparations, 1 mg of calcitonin (salmon) ($C_{145}H_{240}N_{44}O_{48}S_2$) is equivalent to 6000 IU of biological activity.

PRODUCTION

The following requirements apply only to calcitonin (salmon) produced by a method based on rDNA technology.

Prior to release, the following tests are carried out on each batch of calcitonin (salmon), unless exemption has been granted by the competent authority.

www.webofpharma.com

https://thuocngocanh.com/

Host-cell-derived proteins

The limit is approved by the competent authority.

Host-cell or vector-derived DNA

The limit is approved by the competent authority.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

The following requirement applies only to calcitonin (salmon) obtained by chemical synthesis.

B. Amino acid analysis (2.2.56).

Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids taking as equivalent to 1 the sum, divided by 20, of the number of moles of aspartic acid, glutamic acid, proline, glycine, valine, leucine, histidine, arginine and lysine. The values fall within the following limits: aspartic acid: 1.8 to 2.2; glutamic acid: 2.7 to 3.3; proline: 1.7 to 2.3; glycine: 2.7 to 3.3; valine: 0.9 to 1.1; leucine: 4.5 to 5.3; histidine: 0.9 to 1.1; arginine: 0.9 to 1.1; lysine: 1.8 to 2.2; serine: 3.2 to 4.2; threonine: 4.2 to 5.2; tyrosine: 0.7 to 1.1; half-cystine: 1.4 to 2.1.

The following requirement applies only to calcitonin (salmon) produced by a method based on rDNA technology.

C. Peptide mapping (2.2.55).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Prepare a 1 mg/mL solution of the substance to be examined. Transfer 1.0 mL to a clean tube. Add 100 µL of *1 M tris-hydrochloride buffer solution pH 8.0 R* and 20 µL of a freshly prepared 1.0 mg/mL solution of *trypsin for peptide mapping R*. Allow to stand at 2-8 °C for 16-20 h. Stop the reaction by adding 10 µL of a 50 per cent *V/V* solution of *trifluoroacetic acid R*. Cap the vial and mix. Centrifuge the vials to remove air bubbles.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *calcitonin (salmon) CRS* instead of the substance to be examined.

CHROMATOGRAPHIC SEPARATION Liquid chromatography (2.2.29).

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm.

Mobile phase:

— *mobile phase A*: mix 1 mL of *trifluoroacetic acid R* and 1000 mL of *water R*; filter and degas;

— *mobile phase B*: mix 0.850 mL of *trifluoroacetic acid R*, 200 mL of *water R* and 800 mL of *acetonitrile for chromatography R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	100 → 65	0 → 35
50 - 60	65 → 40	35 → 60
60 - 60.1	40 → 0	60 → 100
60.1 - 65.1	0	100
65.1 - 65.2	0 → 100	100 → 0
65.2 - 80.2	100	0

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 214 nm.

Equilibration At initial conditions for at least 15 min. Carry out a blank run using the above-mentioned gradient.

Injection 20 µL.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of calcitonin (salmon) digest supplied with *calcitonin (salmon) CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution: the retention times of the fragment peaks in the chromatogram obtained with the test solution are within 5 per cent of the retention times of the fragments obtained with the reference solution; the peak area ratios of the fragment peaks in the chromatogram obtained with the test solution, normalised to the area of peak T_2, are within 5 per cent of the corresponding peak ratios in the chromatogram obtained with the reference solution.

TESTS

Acetic acid (*2.5.34*)

www.webofpharma.com

https://nhathuocngocanh.com/

4.0 per cent to 15.0 per cent.

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of mobile phases.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure.

The following requirement applies to calcitonin (salmon), whether obtained by chemical synthesis or by a method based on rDNA technology.

A. *Test solution*. Prepare a 1.0 mg/mL solution of the substance to be examined in mobile phase A.

Reference solution Dissolve the contents of a vial of *calcitonin (salmon) CRS* in mobile phase A to obtain a concentration of 1.0 mg/mL.

Resolution solution Dissolve the contents of a vial of *N-acetyl-Cys^{1}-calcitonin CRS* in 400 µL of mobile phase A and add 100 µL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 65 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.26 g of *tetramethylammonium hydroxide R* in 900 mL of *water R*, adjust to pH 2.5 with *phosphoric acid R* and mix with 100 mL of *acetonitrile for chromatography R*; filter and degas;

— *mobile phase B*: dissolve 1.45 g of *tetramethylammonium hydroxide R* in 400 mL of *water R*, adjust to pH 2.5 with *phosphoric acid R* and mix with 600 mL of *acetonitrile for chromatography R*; filter and degas;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	72 → 48	28 → 52
30 - 32	48 → 72	52 → 28
32 - 55	72	28

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to calcitonin (salmon) (retention time = about 20 min): impurity B = about 0.8; impurity C = about 0.9; impurity D = about 1.05; impurity A = about 1.15.

System suitability Resolution solution:

— *resolution*: minimum 5.0 between the peaks due to calcitonin (salmon) and impurity A,

— *symmetry factor*: maximum 2.5 for the peak due to impurity A.

Limits:

— *impurities A, B, C, D*: for each impurity, maximum 3.0 per cent; other unidentified, specified impurities may occur that co-elute with impurities A, B, C and D; the acceptance criterion applies irrespective of whether these impurities co-elute;

— *total*: maximum 5.0 per cent;

— *disregard limit*: 0.1 per cent.

The following requirement applies only to calcitonin (salmon) produced by a method based on rDNA technology.

B. *Test solution*. Prepare a 0.5 mg/mL solution of the substance to be examined. To 1.0 mL of this solution add 100 µL of *0.25 M citrate buffer solution pH 3.0 R*.

Resolution solution Prepare a 1 mg/mL solution of the substance to be examined. Mix 1 volume of the solution and 1 volume of *calcitonin-Gly CRS*. To 1.0 mL of this mixture add 100 µL of *0.25 M citrate buffer solution pH 3.0 R*.

Column:

— *size*: *l* = 0.20 m, Ø = 4.6 mm;

— *stationary phase*: a suitable polysulfoethylaspartamide ion-exchange gel (5 µm).

Mobile phase:

— *mobile phase A*: mix 15 volumes of *acetonitrile for chromatography R* and 85 volumes of a 2.72 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 5.0 with a 600 g/L solution of *potassium hydroxide R*;

— *mobile phase B*: mix 15 volumes of *acetonitrile for chromatography R* and 85 volumes of a solution containing 2.72 g/L of *potassium dihydrogen phosphate R* and 29.22 g/L of *sodium chloride R* adjusted to pH 4.6 with a 600 g/L solution of *potassium hydroxide R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100 → 0	0 → 100
10 - 15	0	100
15 - 15.1	0 → 100	100 → 0

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
15.1 - 22.1	100	0

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 50 µL; rinse the injector with a 40 per cent *V/V* solution of *acetonitrile for chromatography R*.

Relative retention With reference to calcitonin (salmon) (retention time = about 9 min): impurity G = about 0.4; impurity F = about 0.6; impurity E = about 0.9.

System suitability Resolution solution:

— *resolution*: minimum 3.0 between the peaks due to impurity E and calcitonin (salmon).

Limits:

— *impurity E*: maximum 0.6 per cent;

— *impurities F, G*: for each impurity, maximum 0.2 per cent.

Water (2.5.32)

Maximum 10.0 per cent.

Acetic acid and water

Maximum 20 per cent, calculated by adding together the percentage contents of acetic acid and water determined by the methods described above.

Bacterial endotoxins (2.6.14)

Less than 25 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances. Use method A for calcitonin (salmon) obtained by chemical synthesis and method B for calcitonin (salmon) obtained by a method based on rDNA technology.

Calculate the content of calcitonin (salmon) ($C_{145}H_{240}N_{44}O_{48}S_2$) from the area of the principal peak in each of the chromatograms obtained with the test solution and the reference solution and the declared content of $C_{145}H_{240}N_{44}O_{48}S_2$ in *calcitonin (salmon) CRS*. Proceed with tangential integration of the peak areas.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Protected from light at a temperature between 2 °C and 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

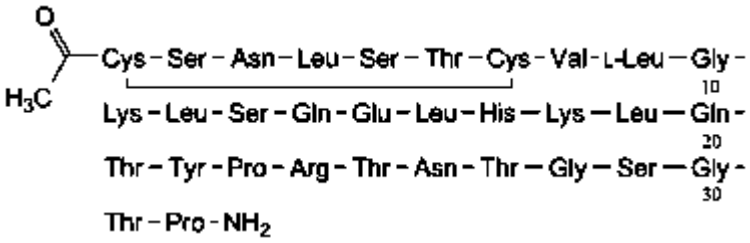
The label states:

— the calcitonin peptide content ($C_{145}H_{240}N_{44}O_{48}S_2$);

— the origin: synthetic or rDNA technology.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

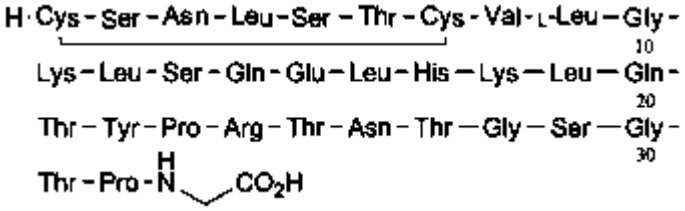


A. acetylcalcitonin (salmon),

B. [9-D-leucine]calcitonin (salmon),

C. des-22-tyrosine-calcitonin (salmon),

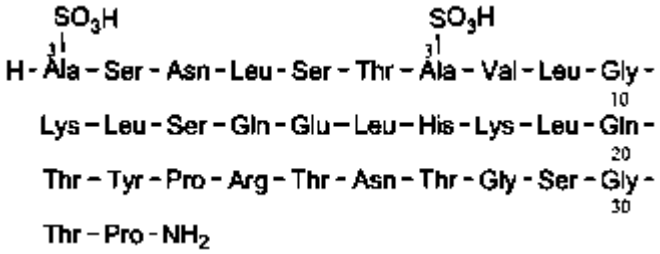
D. *O*-acetylated calcitonin (salmon),



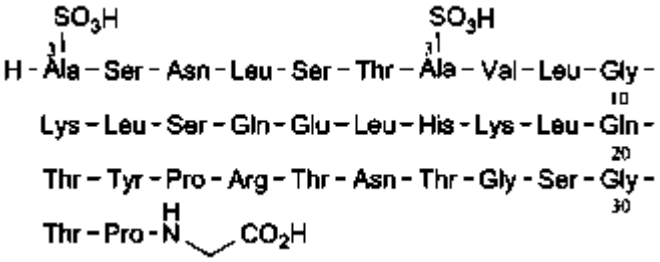
E. salmon calcitoninylglycine,

www.webofpharma.com

https://thuocngocanh.com/



F. [1,7-bis(3-sulfo-L-alanine)]calcitonin (salmon),



G. [1,7-bis(3-sulfo-L-alanine)]calcitoninylglycine (salmon).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcitonin (Salmon) Injection

General Notices

Action and use

Hormone.

DEFINITION

Calcitonin (Salmon) Injection is a sterile solution of Calcitonin (Salmon) in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of calcitonin (salmon), $C_{145}H_{240}N_{44}O_{48}S_2$

90.0 to 115.0% of the stated amount of the peptide.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.9 to 4.5, Appendix V L.

Calcitonin C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection, if necessary, with a 0.1M solution of *sodium dihydrogen orthophosphate* adjusted to pH 4.0 with *orthophosphoric acid* to give a final concentration of 10 µg of calcitonin (salmon) per mL.

(2) 10 µg of *calcitonin (salmon) EPCRS* per mL in a 0.1M solution of *sodium dihydrogen orthophosphate* adjusted to pH 4.0 with *orthophosphoric acid*.

(3) Heat the injection at 75° for 15 hours and, if necessary, dilute as described for solution (1).

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thietbiuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Vydac C18, 300 Å wide pore column for proteins and peptides is suitable).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A 100 volumes of a 0.363% w/v solution of *tetramethylammonium hydroxide pentahydrate* and 150 volumes of *acetonitrile* adjusted to pH 2.5 with *orthophosphoric acid*.

Mobile phase B 50 volumes of *acetonitrile* and 450 volumes of a 0.402% w/v solution of *tetramethyl-ammonium hydroxide pentahydrate* adjusted to pH 2.5 with *orthophosphoric acid*.

Use the following gradient.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-21	35→57	65→43	linear gradient
21-22	57→35	43→65	linear gradient
22-30	35	65	re-equilibration

In the chromatogram obtained with solution (3) the peak due to calcitonin C is the largest peak to elute after the injection buffer salts and before the principal peak with a relative retention to that of calcitonin (salmon) of between 0.5 and 0.6.

SYSTEM SUITABILITY

The test is not valid unless the *resolution factor* between the peaks due to calcitonin C and calcitonin (salmon) in the chromatogram obtained with solution (3) is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to calcitonin C is not greater than 7% by *normalisation*.

Related peptides

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection, if necessary, with mobile phase A to give a final concentration of 10 µg of calcitonin (salmon) per mL.

(2) Dissolve the contents of a vial of N-*acetyl-cys*[1] *calcitonin EPCRS* in 0.4 mL of mobile phase A, dilute to 40 mL with mobile phase A and add 0.1 mL of solution (1).

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 65°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 3.26 g of *tetramethylammonium hydroxide pentahydrate* in 900 mL of *water*, adjust the pH to 2.5 with *orthophosphoric acid* and mix with 100 mL of *acetonitrile for chromatography*.

Mobile phase B Dissolve 1.45 g of *tetramethylammonium hydroxide pentahydrate* in 400 mL of *water*, adjust the pH to 2.5 with *orthophosphoric acid* and mix with 600 mL of *acetonitrile for chromatography*.

Use the following gradient.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	72→48	28→52	linear gradient
30-32	48→72	52→28	linear gradient
32-55	72	28	re-equilibration

When the chromatogram for solution (2) is recorded in the prescribed conditions, the relative retention time of *N*-acetyl-cys[1] calcitonin is about 1.15 relative to the principal peak.

SYSTEM SUITABILITY

The test is not valid unless the *resolution factor* between the peaks corresponding to calcitonin and *N*-acetyl-cys[1] calcitonin is at least 5.0 and the *symmetry factor* for the *N*-acetyl-cys[1] calcitonin peak is not greater than 2.5. If necessary, adjust the initial ratio of A:B in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 3% of the total area of all the peaks;

the sum of the areas of any such peaks is not greater than 5% of the total area of all the peaks by *normalisation*;

disregard any peak with an area less than 0.1 % of that of the principal peak.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method described under the test for Calcitonin C.

Calculate the content of calcitonin (salmon) from the areas of the peak due to calcitonin (salmon) and that of any peak due to calcitonin C, using the declared content of $C_{145}H_{240}N_{44}O_{48}S_2$ in *calcitonin (salmon) EPCRS*.

STORAGE

Calcitonin (Salmon) Injection should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The label states the strength as the number of IU (Units) per mL. The label also states the equivalent number of micrograms of the peptide per mL.

© Crown Copyright 2022

www.webofpharma.com

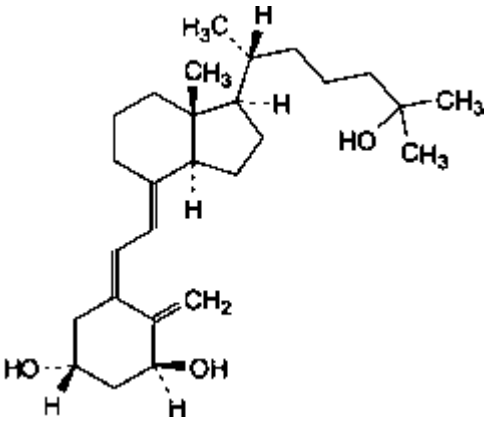
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcitriol

General Notices

(Ph. Eur. monograph 0883)



$C_{27}H_{44}O_3$ 416.6 *32222-06-3*

Action and use

Vitamin D analogue.

Preparation

Calcitriol Capsules

Ph Eur

DEFINITION

(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,25-triol.

Content

97.0 per cent to 103.0 per cent.

A reversible isomerisation to pre-calcitriol takes place in solution, depending on temperature and time. The activity is due to both compounds (see Assay).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white crystals.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in fatty oils.

It is sensitive to air, heat and light.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of calcitriol*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Carry out the test as rapidly as possible, avoiding exposure to actinic light and air.*

Test solution Dissolve 1.00 mg of the substance to be examined without heating in 10.0 mL of the mobile phase.

Reference solution (a) Dissolve 1.00 mg of *calcitriol CRS* without heating in 10.0 mL of the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Heat 2 mL of reference solution (a) at 80 °C for 30 min.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R1* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 450 volumes of a 1.0 g/L solution of *tris(hydroxymethyl)aminomethane R* adjusted to pH 7.0-7.5 with *phosphoric acid R*, and 550 volumes of *acetonitrile R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 50 µL.

Run time Twice the retention time of calcitriol.

Relative retention With reference to calcitriol (retention time = about 14 min): impurity C = about 0.4; pre-calcitriol = about 0.88; impurity A = about 0.95; impurity B = about 1.1.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to pre-calcitriol and calcitriol in the chromatogram obtained with reference solution (c);

— *number of theoretical plates*: minimum 10 000, calculated for the peak due to calcitriol in the chromatogram obtained with reference solution (a).

Limits:

— *impurities A, B, C*: for each impurity, maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to pre-calcitriol.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1 per cent for the peak due to calcitriol after 6 injections.

Calculate the percentage content of $C_{27}H_{44}O_3$ taking into account the assigned content of *calcitriol CRS* and, if necessary, the peak due to pre-calcitriol.

STORAGE

Under nitrogen, in an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

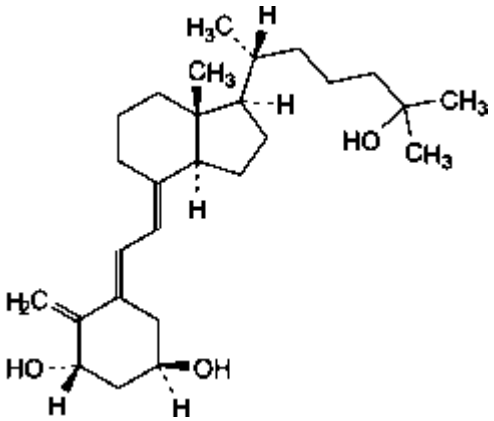
The contents of an opened container are to be used immediately.

IMPURITIES

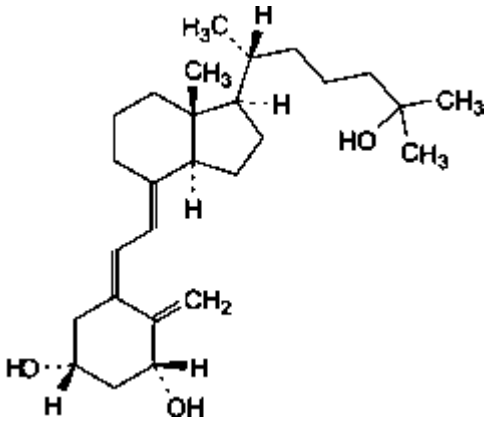
Specified impurities *A, B, C.*

www.webofpharma.com

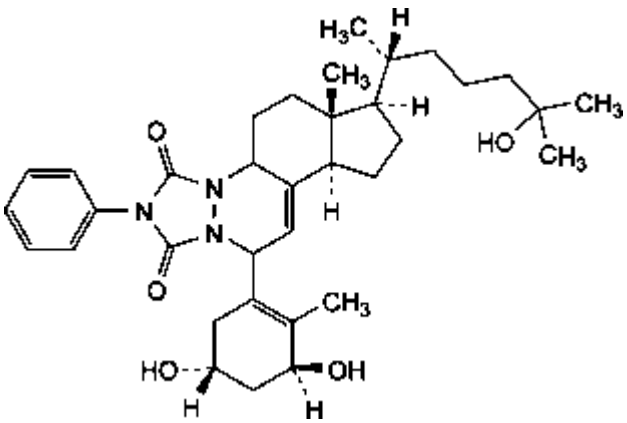
https://thuocngocanh.com/



A. (5*E*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol (*trans*-calcitriol),



B. (5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1β,3β,25-triol (1β-calcitriol),



C. (6a*R*,7*R*,9a*R*)-11-[(3*S*,5*R*)-3,5-dihydroxy-2-methylcyclohex-1-enyl]-7-[(1*R*)-5-hydroxy-1,5-dimethylhexyl]-6a-methyl-2-phenyl-5,6,6a,7,8,9,9a,11-octahydro-1*H*,4a*H*-cyclopenta[*f*][1,2,4]triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (triazoline adduct of pre-calcitriol).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcitriol Capsules

General Notices

Action and use

Vitamin D analogue.

DEFINITION

Calcitriol Capsules contain a solution of Calcitriol in a suitable fixed oil.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of calcitriol, $C_{27}H_{44}O_3$

90.0 to 110.0% of the stated amount.

A reversible isomerisation to pre-calcitriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

IDENTIFICATION

In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to calcitriol in the chromatogram obtained with solution (2).

ASSAY

Mix the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For capsules containing 0.25 µg of Calcitriol or less, prepare solution (1) in the following manner:

(1) Use an undiluted quantity of the mixed capsule content.

For capsules containing more than 0.25 µg of Calcitriol, prepare solution (1) in the following manner:

(1) To a quantity of the mixed capsule content containing 1.5 µg of Calcitriol, add sufficient mobile phase to produce 1 mL.
(2) 0.00015% w/v of *calcitriol EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Lichrosorb Si60 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

(g) If necessary, adjust the composition of the mobile phase so that the principal peak in the chromatogram obtained with solution (1) is clearly separated from the tail of the peak due to the excipient (fixed oil).

MOBILE PHASE

1 volume of *propan-1-ol*, 2 volumes of *methanol*, 40 volumes of *hexane* and 60 volumes of *ethyl acetate*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (1), the peak due to calcitriol is clearly separated from the peak due to the fixed oil.

DETERMINATION OF CONTENT

Combine the peak areas of calcitriol and pre-calcitriol in solutions (1) and (2) respectively. Calculate the content of calcitriol, $C_{27}H_{44}O_3$ in the capsules, using the declared content of $C_{27}H_{44}O_3$ in *calcitriol EPCRS*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

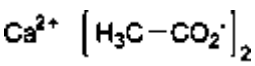
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Calcium Acetate

General Notices

(Ph. Eur. monograph 2128)



$C_4H_6CaO_4$ 158.2 *62-54-4*

Action and use

Used in solutions for haemodialysis and peritoneal dialysis.

Ph Eur

DEFINITION

Calcium diacetate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. It gives reaction (b) of calcium (*2.3.1*).

B. It gives reaction (b) of acetates (*2.3.1*).

TESTS

Solution S

https://thuocngocanh.com/

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

7.2 to 8.2.

Dilute 5.0 mL of solution S to 10.0 mL with *carbon dioxide-free water R*.

Readily oxidisable substances

Dissolve 2.0 g in boiling *water R* and dilute to 100 mL with boiling *water R*. Add a few glass beads, 6 mL of *5 M sulfuric acid R* and 0.3 mL of a 3.2 g/L solution of *potassium permanganate R*. Mix, boil gently for 5 min and allow the precipitate to settle. The pink colour in the supernatant is not completely discharged.

Chlorides, nitrates, sulfates

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 5.00 g of the substance to be examined in 50 mL of *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dilute 20.0 mL of test solution (a) to 100.0 mL with *water for chromatography R*.

Reference solution To 20.0 mL of test solution (a) add 8.0 mL of *chloride standard solution (50 ppm Cl) R*, 1.0 mL of *nitrate standard solution (10 ppm NO_3) R* and 6.0 mL of *sulfate standard solution (100 ppm SO_4) R* and dilute to 100.0 mL with *water for chromatography R*.

Blank solution *water for chromatography R*.

Pre-concentration column Connected with a suitable cation-exchange module. Use *water for chromatography R* to transfer the injected solution to the pre-concentration column.

— *size*: *l* = 0.013 m, Ø = 4 mm;

— *stationary phase*: *strong anion-exchange polymethacrylate resin for chromatography R* (65 µm).

Precolumn:

— *size*: *l* = 0.05 m, Ø = 4 mm;

— *stationary phase*: *strong anion-exchange poly(vinyl alcohol) resin for chromatography R* (5 µm);

— *temperature*: 40 °C.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *strong anion-exchange poly(vinyl alcohol) resin for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Dissolve 0.382 g of *anhydrous sodium carbonate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent.

Flow rate 0.7 mL/min.

Detection Conductivity detector equipped with a suitable anion suppressor.

Injection 20 µL of test solution (b), the reference solution and the blank solution.

Run time 1.3 times the retention time of sulfate.

Retention time Chloride = about 12 min; nitrate = about 25 min; sulfate = about 33 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the area of the peak due to nitrate determined on 5 injections;

— *resolution*: minimum 5.0 between the peaks due to nitrate and sulfate.

Calculation of contents:

— for chlorides, nitrates and sulfates, use the concentration of the corresponding ions in the reference solution; correct the area of the peaks due to chloride, nitrate and sulfate in the chromatogram obtained with the reference solution by subtracting the area of the corresponding peaks in the chromatogram obtained with test solution (b).

Limits:

— *chlorides*: maximum 330 ppm;

— *nitrates*: maximum 10 ppm;

— *sulfates*: maximum 600 ppm.

Fluorides

Maximum 50 ppm.

Potentiometry (*2.2.36, Method I*).

Test solution In a 50 mL volumetric flask, dissolve 0.200 g in a 10.3 g/L solution of *hydrochloric acid R*, add 5.0 mL of *fluoride standard solution (1 ppm F) R* and dilute to 50.0 mL with a 10.3 g/L solution of *hydrochloric acid R*. To 20.0 mL of the solution add 20.0 mL of *total-ionic-strength-adjustment buffer R* and 3 mL of an 82 g/L solution of *anhydrous sodium acetate R*. Adjust to pH 5.2 with *ammonia R* and dilute to 50.0 mL with *distilled water R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions To 0.25 mL, 0.5 mL, 0.75 mL and 1.0 mL of *fluoride standard solution (10 ppm F) R* add 20.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50.0 mL with *distilled water R*.

Indicator electrode Fluoride selective.

Reference electrode Silver-silver chloride.

Take into account the addition of fluoride to the test solution for the calculation.

Aluminium (*2.4.17*)

Maximum 1 ppm, if intended for use in the manufacture of peritoneal dialysis solutions, haemofiltration solutions or haemodialysis solutions.

Test solution Dissolve 4.0 g of the substance to be examined in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Iron (*2.4.9*)

Maximum 20 ppm, if intended for use in the manufacture of parenteral preparations or haemodialysis solutions.

Dilute 5 mL of solution S to 10 mL of *water R*.

Magnesium

Maximum 500 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using *magnesium standard solution (0.1 per cent Mg) R*, diluted as necessary with *water R*.

Source Magnesium hollow-cathode lamp.

Wavelength 285.2 nm.

Atomisation device Air-acetylene flame.

Potassium

Maximum 500 ppm, if intended for use in the manufacture of parenteral preparations or haemodialysis solutions.

Atomic emission spectrometry (*2.2.22, Method II*).

Test solution Dissolve 1.00 g of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions Prepare the reference solutions using *potassium standard solution (0.2 per cent K) R*, diluted as necessary with *water R*.

Wavelength 766.5 nm.

Sodium

Maximum 500 ppm, if intended for use in the manufacture of parenteral preparations or haemodialysis solutions.

Atomic emission spectrometry (*2.2.22, Method II*).

Test solution Dissolve 1.00 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluted as necessary with *water R*.

Wavelength 589 nm.

Strontium

Maximum 500 ppm, if intended for use in the manufacture of parenteral preparations or haemodialysis solutions.

Atomic emission spectrometry (*2.2.22, Method II*).

Test solution Dissolve 2.00 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using *strontium standard solution (1.0 per cent Sr) R*, diluted as necessary with *water R*.

Wavelength 460.7 nm.

Water (*2.5.12*)

Maximum 7.0 per cent, determined on 0.100 g. Add 2 mL of *anhydrous acetic acid R* to the titration vessel in addition to the methanol. Clean the titration vessel after each determination.

ASSAY

Dissolve 0.150 g in 100 mL of *water R* and carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 15.82 mg of $C_4H_6CaO_4$.

STORAGE

In an airtight container.

LABELLING

www.webofpharma.com

https://thuvienthuocngocanh.com/

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations, peritoneal dialysis solutions, haemofiltration solutions or haemodialysis solutions.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium and Colecalciferol Chewable Tablets

General Notices

Chewable Calcium and Colecalciferol Tablets

DEFINITION

Calcium and Colecalciferol Chewable Tablets contain Calcium Carbonate and Colecalciferol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of calcium

85.0 to 115.0% of the stated amount.

Content of colecalciferol, $C_{27}H_{44}O$

90.0 to 120.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 µg of colecalciferol with 20 mL of the mobile phase with the aid of ultrasound for 15 minutes, cool to room temperature, centrifuge and use the supernatant liquid.

(2) 0.0001% w/v each of *colecalciferol BPCRS* and *ergocalciferol BPCRS* in the mobile phase.

(3) 0.0001% w/v of *colecalciferol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

10 volumes of *water* and 90 volumes of *methanol*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the two principal peaks is at least 1.4. If necessary, adjust the composition of the mobile phase to obtain the required resolution.

CONFIRMATION

A peak in the chromatogram obtained with solution (1) has the same retention time as the peak due to colecalciferol in the chromatogram obtained with solution (3).

B. Shake a quantity of the powdered tablets containing the equivalent of 10 mg of calcium with 50 mL of *water* and filter. The solution yields reaction A characteristic of *calcium salts*, Appendix VI.

TESTS

Disintegration

The requirement for Disintegration does not apply to Calcium and Colecalciferol Chewable Tablets.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Colecalciferol comply with the requirements stated under Tablets, with respect to the content of Colecalciferol, using the following method of analysis. Carry out the following procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 15 mL of *methanol (90%)*, mix with the aid of ultrasound until the tablet is dispersed and then for a further 5 minutes, dilute to 20 mL with *methanol (90%)*, mix, centrifuge and filter through a glass-fibre filter (Whatman GF/C is suitable).
(2) 0.00005% w/v of *colecalciferol BPCRS* in *methanol (90%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{44}O$ in each tablet using the declared content of $C_{27}H_{44}O$ in *colecalciferol BPCRS*.

ASSAY

For calcium

Weigh and powder 20 tablets. To a quantity of the powder containing the equivalent of 50 mg of calcium add 50 mL of *water* and 5 mL of *hydrochloric acid*. Heat the dispersion gently to boiling and continue to boil for about 2 minutes. Allow to cool and add 50 mL of 0.05M *disodium edetate VS*. Neutralise the solution using 2M *sodium hydroxide*, add 10 mL of *ammonia buffer pH 10.9* and 50 mL of *water*. Titrate the excess of disodium edetate with 0.05M *zinc chloride VS* using *mordant black II solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.004 mg of Ca.

For colecalciferol

www.webofpharma.com

https://thuocngocanh.com/

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, protect from light throughout the procedure and using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 mg of Colecalciferol with about 170 mL of *methanol* (*90*%) for 5 minutes and then mix with ultrasound for 5 minutes, dilute to 200 mL with *methanol* (*90*%), mix, centrifuge and filter through a glass-fibre filter (Whatman GF/C is suitable).

(2) 0.00005% w/v of *colecalciferol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 264 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

3 volumes of *water* and 97 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{44}O$ in the tablets using the declared content of $C_{27}H_{44}O$ in *colecalciferol BPCRS*.

LABELLING

The label states (1) the equivalent number of IU (Units) of antirachitic activity (vitamin D); (2) the equivalent amount of calcium.

Each microgram of Colecalciferol is equivalent to 40 IU of antirachitic activity (vitamin D).

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium and Colecalciferol Tablets

General Notices

DEFINITION

Calcium and Colecalciferol Tablets contain Calcium Carbonate and Colecalciferol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of calcium

85.0 to 115.0% of the stated amount.

Content of colecalciferol, $C_{27}H_{44}O$

90.0 to 120.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 µg of Colecalciferol with 20 mL of the mobile phase with the aid of ultrasound for 15 minutes, cool to room temperature, centrifuge and use the supernatant liquid.

(2) 0.0001% w/v each of *colecalciferol BPCRS* and *ergocalciferol BPCRS* in the mobile phase.

(3) 0.0001% w/v of *colecalciferol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

10 volumes of *water* and 90 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the two principal peaks is at least 1.4. If necessary, adjust the composition of the mobile phase to obtain the required resolution.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

A peak in the chromatogram obtained with solution (1) has the same retention time as the peak due to colecalciferol in the chromatogram obtained with solution (3).

B. Shake a quantity of the powdered tablets containing the equivalent of 10 mg of calcium with 50 mL of *water* and filter. The solution yields reaction A characteristic of *calcium salts*, Appendix VI.

TESTS

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Colecalciferol comply with the requirements stated under Tablets, with respect to the content of Colecalciferol, using the following method of analysis. Carry out the following procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 15 mL of *methanol (90%)*, mix with the aid of ultrasound until the tablet is dispersed and then for a further 5 minutes, dilute to 20 mL with *methanol (90%)*, mix, centrifuge and filter through a glass-fibre filter (Whatman GF/C is suitable).
(2) 0.00005% w/v of *colecalciferol BPCRS* in *methanol (90%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{44}O$ in each tablet using the declared content of $C_{27}H_{44}O$ in *colecalciferol BPCRS*.

ASSAY

For calcium

Weigh and powder 20 tablets. To a quantity of the powder containing the equivalent of 50 mg of calcium add 50 mL of *water* and 5 mL of *hydrochloric acid*. Heat the dispersion gently to boiling and continue to boil for about 2 minutes. Allow to cool and add 50 mL of 0.05M *disodium edetate VS*. Neutralise the solution using 2M *sodium hydroxide*, add 10 mL of *ammonia buffer pH 10.9* and 50 mL of *water*. Titrate the excess of disodium edetate with 0.05M *zinc chloride VS* using *mordant black II solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.004 mg of Ca.

For colecalciferol

Carry out the following procedure protected from light. Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 mg of Colecalciferol with about 170 mL of *methanol (90%)* for 5 minutes and then mix with ultrasound for 5 minutes, dilute to 200 mL with *methanol (90%)*, mix, centrifuge and filter through a glass-fibre filter (Whatman GF/C is suitable).
(2) 0.00005% w/v of *colecalciferol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thietbiuocngocanh.com/

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 264 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

3 volumes of *water* and 97 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{44}O$ in the tablets using the declared content of $C_{27}H_{44}O$ in *colecalciferol BPCRS*.

LABELLING

The label states (1) the equivalent number of IU (Units) of antirachitic activity (vitamin D); (2) the equivalent amount of calcium.

Each microgram of Colecalciferol is equivalent to 40 IU of antirachitic activity (vitamin D).

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium and Ergocalciferol Chewable Tablets

General Notices

Chewable Calcium and Ergocalciferol Tablets

DEFINITION

Calcium and Ergocalciferol Chewable Tablets contain Calcium Lactate Pentahydrate, Calcium Phosphate and Ergocalciferol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of calcium

85.0 to 115.0% of the stated amount.

Content of ergocalciferol, $C_{28}H_{44}O$

90.0 to 120.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 µg of ergocalciferol with 20 mL of the mobile phase with the aid of ultrasound for 15 minutes, cool to room temperature, centrifuge and use the supernatant liquid.

(2) 0.0001% w/v each of *colecalciferol BPCRS* and *ergocalciferol BPCRS* in the mobile phase.

(3) 0.0001% w/v of *ergocalciferol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

10 volumes of *water* and 90 volumes of *methanol*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the two principal peaks is at least 1.4. If necessary, adjust the composition of the mobile phase to obtain the required resolution.

CONFIRMATION

The chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to ergocalciferol in the chromatogram obtained with solution (3).

B. Disperse a quantity of the powdered tablets containing the equivalent of 10 mg of calcium in 5 mL of *water* and filter. The filtrate yields reaction A characteristic of *lactates*, Appendix VI.

C. Warm a quantity of the powdered tablets containing the equivalent of 90 mg of calcium with 10 mL of 2M *nitric acid*, cool and filter. Add 10 mL of *ammonium molybdate solution* to the filtrate. A yellow precipitate is produced, characteristic of phosphates.

D. Shake a quantity of the powdered tablets containing the equivalent of 10 mg of calcium with 50 mL of *water* and filter. The solution yields reaction A characteristic of *calcium salts*, Appendix VI.

TESTS

Disintegration

The requirement for Disintegration does not apply to Calcium and Ergocalciferol Chewable Tablets.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Ergocalciferol comply with the requirements stated under Tablets, with respect to the content of Ergocalciferol, using the following method of analysis. Carry out the following procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 15 mL of *methanol (90%)*, mix with the aid of ultrasound until the tablet is dispersed and then for a further 5 minutes, dilute to 20 mL with *methanol (90%)*, mix, centrifuge and filter through a glass-fibre filter (Whatman GF/C is suitable).

(2) 0.00005% w/v of *ergocalciferol BPCRS* in *methanol (90%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay for ergocalciferol may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{44}O$ in each tablet using the declared content of $C_{28}H_{44}O$ in *ergocalciferol BPCRS*.

ASSAY

For calcium

Weigh and powder 20 tablets. To a quantity of the powder containing the equivalent of 50 mg of calcium add 50 mL of *water* and 5 mL of *hydrochloric acid*. Heat the dispersion gently to boiling and continue for about 2 minutes. Allow to cool and add 50 mL of 0.05M *disodium edetate VS*. Neutralise the solution using 2M *sodium hydroxide*, add 10 mL of *ammonia buffer pH 10.9* and 50 mL of *water*. Titrate the

www.webofpharma.com

https://thuocngocanh.com/

excess of disodium edetate with 0.05M *zinc chloride VS* using *mordant black II solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.004 mg of Ca.

For ergocalciferol

Carry out the following procedure protected from light. Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 mg of Ergocalciferol with about 170 mL of *methanol (90%)* for 5 minutes. Mix with the aid of ultrasound for a further 5 minutes, dilute to 200 mL with *methanol (90%)*, centrifuge and filter through a glass fibre filter (Whatman GF/C is suitable).

(2) 0.00005% w/v of *ergocalciferol BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 264 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

3 volumes of *water* and 97 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{28}H_{44}O$ in the tablets using the declared content of $C_{28}H_{44}O$ in *ergocalciferol BPCRS*.

LABELLING

The label states (1) the equivalent number of IU (Units) of antirachitic activity (vitamin D); (2) the equivalent amount of calcium.

Each microgram of Ergocalciferol is equivalent to 40 IU of antirachitic activity (vitamin D).

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

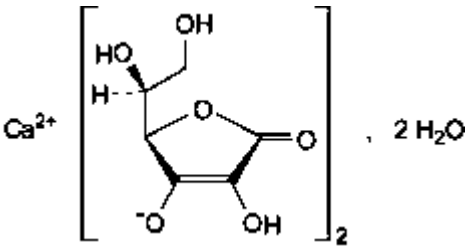
This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Calcium Ascorbate Dihydrate

General Notices

Calcium Ascorbate

(Ph. Eur. monograph 1182)



$C_{12}H_{14}CaO_{12},2H_2O$ 426.3 *5743-28-2*

Action and use

Excipient.

Ph Eur

DEFINITION

Calcium di[(2*R*)-2-[(1*S*)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate] dihydrate.

Content

99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent) and in heptane.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, B, E.

Second identification: A, C, D, E.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *calcium ascorbate dihydrate CRS*.

C. Dilute 1 mL of solution S (see Tests) to 10 mL with *water R*. To 2 mL of the solution add 0.2 mL of a 100 g/L solution of *ferrous sulfate R*. A deep violet colour develops.

D. To 1 mL of solution S add 0.2 mL of *dilute nitric acid R* and 0.2 mL of *silver nitrate solution R2*. A grey precipitate is formed.

E. The substance gives reaction (b) of calcium (2.3.1).

TESTS

Solution S

Dissolve 5.00 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*). Examine the colour of the solution immediately after preparation.

pH (2.2.3)

6.8 to 7.4 for solution S.

Specific optical rotation (2.2.7)

+ 95 to + 97 (dried substance), determined using freshly prepared solution S.

Related substances

Liquid chromatography (2.2.29). Prepare the solutions immediately before use.

Solution A A 17 g/L solution of *potassium dihydrogen phosphate R*.

Phosphate buffer solution Dissolve 6.8 g of *potassium dihydrogen phosphate R* in *water for chromatography R* and dilute to about 200 mL with the same solvent. Filter through a membrane filter (nominal pore size 0.45 µm) and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 0.500 g of the substance to be examined in 2.5 mL of *water R* and sonicate for 4 min. After complete dissolution, add 2.5 mL of solution A and dilute to 10.0 mL with *acetonitrile R*. Centrifuge for 5 min at 1500-2000 *g*. Inject the clear supernatant.

Reference solution (a) Dissolve 10.0 mg of *ascorbic acid impurity C CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 5.0 mg of *ascorbic acid impurity D CRS* and 5.0 mg of *ascorbic acid CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1 mL of the test solution to 200 mL with the mobile phase. Mix 1 mL of this solution and 1 mL of reference solution (a).

Reference solution (d) Dilute 2.5 mL of reference solution (a) to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase Phosphate buffer solution, *acetonitrile R1* (25:75 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 4.5 times the retention time of ascorbic acid.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to ascorbic acid (retention time = about 9 min): impurity D = about 0.5; impurity C = about 1.45.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to ascorbic acid and impurity C in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 20 for the peak due to impurity C in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— for impurity C, use the concentration of impurity C in reference solution (d);

— for impurity D, use the concentration of impurity D in reference solution (b);

— for impurities other than C and D, use the concentration of ascorbic acid in reference solution (b).

Limits:

— *impurities C, D*: for each impurity, maximum 0.15 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *sum of impurities other than C and D*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Fluorides

Maximum 10 ppm.

Potentiometry (*2.2.36, Method I*).

Test solution In a 50 mL volumetric flask, dissolve 1.000 g in a 10.3 g/L solution of *hydrochloric acid R*, add 5.0 mL of *fluoride standard solution (1 ppm F) R* and dilute to 50.0 mL with a 10.3 g/L solution of *hydrochloric acid R*. To 20.0 mL of the solution add 20.0 mL of *total-ionic-strength-adjustment buffer R* and 3 mL of an 82 g/L solution of *anhydrous sodium acetate R*. Adjust to pH 5.2 with *ammonia R* and dilute to 50.0 mL with *distilled water R*.

Reference solutions To 0.25 mL, 0.5 mL, 1.0 mL, 2.0 mL and 5.0 mL of *fluoride standard solution (10 ppm F) R* add 20.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50.0 mL with *distilled water R*.

Indicator electrode Fluoride selective.

Reference electrode Silver-silver chloride.

Take into account the addition of fluoride to the test solution for the calculation.

Iron

Maximum 2 ppm.

Atomic absorption spectrometry (*2.2.23*).

Test solution Dissolve 5.0 g in a 9.7 g/L solution of *nitric acid R* and dilute to 25.0 mL with the same acid solution.

Reference solutions Prepare the reference solutions using *iron standard solution (10 ppm Fe) R*, diluting with a 9.7 g/L solution of *nitric acid R*.

Source Iron hollow-cathode lamp.

Wavelength 248.3 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 0.1 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 80.0 mg in a mixture of 10 mL of *dilute sulfuric acid R* and 80 mL of *carbon dioxide-free water R*. Add 1 mL of *starch solution R*. Titrate with *0.05 M iodine* until a persistent violet-blue colour is obtained.

1 mL of *0.05 M iodine* is equivalent to 10.66 mg of $C_{12}H_{14}CaO_{12},2H_2O$.

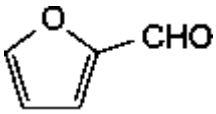
STORAGE

In a non-metallic container, protected from light.

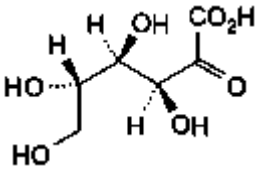
IMPURITIES

Specified impurities C, D.

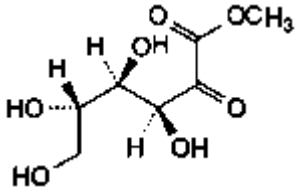
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, E, F.



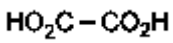
A. furan-2-carbaldehyde (furfural),



C. L-*xylo*-hex-2-ulosonic acid (L-sorbosonic acid),



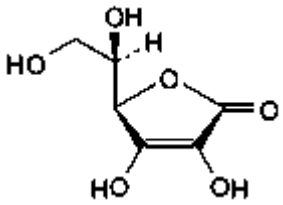
D. methyl L-*xylo*-hex-2-ulosonate (methyl L-sorbosonate),



E. oxalic acid,

www.webofpharma.com

https://thuocngocanh.com/



F. (5*R*)-5-[(1*R*)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Carbonate

General Notices

(Ph. Eur. monograph 0014)

$CaCO_3$ 100.1 *471-34-1*

Action and use

Antacid.

Preparations

Calcium Carbonate Chewable Tablets

Calcium Carbonate Oral Suspension

Calcium and Colecalciferol Tablets

Calcium and Colecalciferol Chewable Tablets

Ph Eur

DEFINITION

Content

98.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water.

IDENTIFICATION

A. It gives the reaction of carbonates (*2.3.1*).

B. 0.2 mL of solution S (see Tests) gives reaction (b) of calcium (*2.3.1*).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 5.0 g in 80 mL of *dilute acetic acid R*. When the effervescence ceases, boil for 2 min. Allow to cool, dilute to 100 mL with *dilute acetic acid R* and filter, if necessary, through a sintered-glass filter (2.1.2). Keep the residue for the test for substances insoluble in acetic acid.

Substances insoluble in acetic acid

Maximum 0.2 per cent.

Wash any residue obtained during the preparation of solution S with 4 quantities, each of 5 mL, of hot *water R* and dry at 100-105 °C for 1 h. The residue weighs a maximum of 10 mg.

Chlorides (2.4.4)

Maximum 330 ppm.

Dilute 3 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 0.25 per cent.

Dilute 1.2 mL of solution S to 15 mL with *distilled water R*.

Iron (2.4.9)

Maximum 200 ppm.

Dissolve 50 mg in 5 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*.

Magnesium and alkali metals

Maximum 1.5 per cent.

Dissolve 1.0 g in 12 mL of *dilute hydrochloric acid R*. Boil the solution for about 2 min and add 20 mL of *water R*, 1 g of *ammonium chloride R* and 0.1 mL of *methyl red solution R*. Add *dilute ammonia R1* until the colour of the indicator changes and then add 2 mL in excess. Heat to boiling and add 50 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 100 mL with *water R* and filter through a suitable filter. To 50 mL of the filtrate add 0.25 mL of *sulfuric acid R*. Evaporate to dryness on a water-bath and ignite to constant mass at 600 ± 50 °C. The residue weighs a maximum of 7.5 mg.

Loss on drying (2.2.32)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 200 ± 10 °C.

ASSAY

Dissolve 0.150 g in a mixture of 3 mL of *dilute hydrochloric acid R* and 20 mL of *water R*. Boil for 2 min, allow to cool and dilute to 50 mL with *water R*. Carry out the complexometric titration of calcium (2.5.11).

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *0.1 M sodium edetate* is equivalent to 10.01 mg of $CaCO_3$.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for calcium carbonate used as filler in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*)

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Carbonate and Heavy Magnesium Carbonate Chewable Tablets

General Notices

Chewable Calcium Carbonate and Heavy Magnesium Carbonate Tablets

Action and use

Antacid.

DEFINITION

Calcium Carbonate and Heavy Magnesium Carbonate Chewable Tablets contain Calcium Carbonate and Heavy Magnesium Carbonate. They may be flavoured.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of Calcium, Ca

95.0 to 105.0% of the stated amount.

Content of magnesium, Mg

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, solution (1) exhibits a similar absorption to the standard solutions at 422.7 nm (calcium).

B. In the Assay, solution (3) exhibits a similar absorption to the standard solutions at 285.2 nm (magnesium).

C. The powdered tablets yield reaction B characteristic of *calcium salts*, Appendix VI.

D. The powdered tablets yield reaction B characteristic of *magnesium* and *magnesium salts*, Appendix VI.

E. The powdered tablets yield the reactions characteristic of *carbonates*, Appendix VI.

TESTS

Disintegration

The requirement for Disintegration does not apply to Calcium Carbonate and Heavy Magnesium Carbonate Chewable Tablets.

ASSAY

For calcium

www.webofpharma.com

https://thuocngocanh.com/

Weigh and powder 20 tablets. For solution (1) disperse a quantity of the powdered tablets containing the equivalent of 0.272 g of calcium in 10 mL of *6M hydrochloric acid*, stir for 15 minutes, and add sufficient *water* to produce 500 mL, mix and filter. To 1 volume of the filtrate add 5 volumes of *lanthanum trioxide solution* and dilute to 100 volumes with *water*.

Prepare the standard solutions using a suitable volume of *calcium standard solution (1000 ppm Ca)* add 10 mL of *6M hydrochloric acid*, and sufficient *water* to produce 500 mL, mix and filter. To 1 volume of the filtrate add 5 volumes of *lanthanum trioxide solution* and dilute to 100 volumes with *water*.

For solution (2) to 10 mL of *6M hydrochloric acid* add sufficient *water* to produce 500 mL, mix and filter. To 1 volume of the filtrate add 5 volumes of *lanthanum trioxide solution* and dilute to 100 volumes with *water*.

Determine the total content of calcium in solution (1) by Method I for *atomic absorption spectrophotometry*, Appendix II D, measuring at 422.7 nm using the standard solutions and solution (2) as the blank.

For magnesium

Weigh and powder 20 tablets. For solution (3) disperse a quantity of the powdered tablets containing the equivalent of 22 mg of magnesium in 10 mL of *6M hydrochloric acid*, stir for 15 minutes and add sufficient *water* to produce 500 mL, mix and filter. To 1 volume of the filtrate add 5 volumes of *lanthanum trioxide solution* and dilute to 100 volumes with *water*.

Prepare the standard solutions using a suitable volume of *magnesium standard solution (100 ppm Mg),* add 10 mL of *6M hydrochloric acid* and sufficient *water* to produce 500 mL, mix and filter. To 1 volume of the filtrate add 5 volumes of *lanthanum trioxide solution* and dilute to 100 volumes with *water*.

Determine the total content of magnesium in solution (3) by Method I for *atomic absorption spectrophotometry*, Appendix II D, measuring at 285.2 nm using the standard solutions and solution (2) as the blank.

STORAGE

Calcium Carbonate and Heavy Magnesium Carbonate Chewable Tablets should be protected from moisture.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of calcium and magnesium.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Carbonate Chewable Tablets

General Notices

Chewable Calcium Carbonate Tablets

DEFINITION

Calcium Carbonate Chewable Tablets contain Calcium Carbonate. They may be flavoured.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of calcium, Ca

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The powdered tablets yield reaction B characteristic of *calcium salts*, Appendix VI.

B. The powdered tablets yield the reactions characteristic of *carbonates*, Appendix VI.

TESTS

Disintegration

The requirement for Disintegration does not apply to Calcium Carbonate Chewable Tablets.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing the equivalent of 0.25 g of calcium add 50 mL of *water* and 5 mL of *hydrochloric acid*. Heat the dispersion gently to boiling and continue to boil for about 2 minutes. Allow to cool, add sufficient *water* to produce 250 mL and filter, if necessary. To 50 mL of this solution add 50 mL of 0.05M *disodium edetate VS*. Neutralise the solution using 2M *sodium hydroxide* and add 10 mL of *ammonia buffer pH 10.9* and 50 mL of *water*. Titrate the excess of disodium edetate with 0.05M *zinc chloride VS* using *mordant black II solution* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 2.004 mg of Ca.

STORAGE

Calcium Carbonate Chewable Tablets should be protected from moisture.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of calcium.

www.webofpharma.com

https://thuathuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Carbonate Oral Suspension

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Phosphate binder; treatment of hyperphosphataemia.

DEFINITION

Calcium Carbonate Oral Suspension is a suspension of Calcium Carbonate in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of calcium carbonate, $CaCO_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

It may be necessary to add a drop of a suitable antifoaming agent to a volume of the oral suspension before carrying out the following tests.

A. Mix 1 volume of the oral suspension with 1 volume of *water* and filter. The filtrate yields reaction C characteristic of *calcium salts*, Appendix VI.

B. Dilute a volume of the oral suspension containing 0.6 g of Calcium Carbonate to 2 volumes with *2M hydrochloric acid*. The resulting solution yields reaction A characteristic of *carbonates*, Appendix VI.

TESTS

Acidity or alkalinity

pH 7.0 to 8.7, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

ASSAY

It may be necessary to add one or two drops of a suitable antifoaming agent to the oral suspension before carrying out the Assay.

www.webofpharma.com

https://thuocngocanh.com/

To a weighed quantity of the oral suspension containing 0.15 g of Calcium Carbonate add 3 mL of *dilute hydrochloric acid* and 20 mL of *water*. Boil for 2 minutes, allow to cool and dilute to 50 mL with *water*. Carry out the *complexometric titration of calcium*, Appendix VIII D. Determine the *weight per ml* of the oral suspension, Appendix V G, and calculate the content of $CaCO_3$, weight in volume.

Each mL of *0.1M sodium edetate* is equivalent to 10.01 mg of $CaCO_3$.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Calcium Chloride Dihydrate

General Notices

(Ph. Eur. monograph 0015)

$CaCl_2,2H_2O$ 147.0 *10035-04-8*

Preparations

Calcium Chloride Injection

Compound Sodium Lactate Infusion

Ph Eur

DEFINITION

Content

97.0 per cent to 103.0 per cent of $CaCl_2,2H_2O$.

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

B. It gives reaction (b) of calcium (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Solution S

www.webofpharma.com

https://thuvienthuocngocanh.com/

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of freshly prepared solution S add 0.1 mL of *phenolphthalein solution R*. If the solution is pink, not more than 0.2 mL of *0.01 M hydrochloric acid* is required to discharge the colour and if the solution is colourless, not more than 0.2 mL of *0.01 M sodium hydroxide* is required to turn it pink.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Aluminium

To 10 mL of solution S add 2 mL of *ammonium chloride solution R* and 1 mL of *dilute ammonia R1* and boil the solution. No turbidity or precipitate is formed.

If intended for use in the manufacture of dialysis solutions, the above test is replaced by the following test for aluminium (*2.4.17*): maximum 1 ppm.

Prescribed solution Dissolve 4 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Magnesium and alkali metals

Maximum 0.5 per cent.

To a mixture of 20 mL of solution S and 80 mL of *water R* add 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*, heat to boiling and pour into the boiling solution a hot solution of 5 g of *ammonium oxalate R* in 75 mL of *water R*. Allow to stand for 4 h, dilute to 200 mL with *water R* and filter through a suitable filter. To 100 mL of the filtrate add 0.5 mL of *sulfuric acid R*. Evaporate to dryness on a water-bath and ignite to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

ASSAY

Dissolve 0.280 g in 100 mL of *water R* and carry out the complexometric titration of calcium (*2.5.11*).

www.webofpharma.com

https://thuvienthuocngocanh.com/

1 mL of *0.1 M sodium edetate* is equivalent to 14.70 mg of $CaCl_2,2H_2O$.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Calcium Chloride Hexahydrate

General Notices

(Ph. Eur. monograph 0707)

$CaCl_2,6H_2O$ 219.1 *7774-34-7*

Ph Eur

DEFINITION

Content

97.0 per cent to 103.0 per cent of $CaCl_2,6H_2O$.

CHARACTERS

Appearance

White or almost white, crystalline mass or colourless crystals.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

It solidifies at about 29 °C.

IDENTIFICATION

A. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

B. It gives reaction (b) of calcium (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Solution S

Dissolve 15.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of freshly prepared solution S add 0.1 mL of *phenolphthalein solution R*. If the solution is pink, not more than 0.2 mL of *0.01 M hydrochloric acid* is required to discharge the colour and if the solution is colourless, not more than 0.2 mL of *0.01 M sodium hydroxide* is required to turn it pink.

Sulfates (2.4.13)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Aluminium

To 10 mL of solution S add 2 mL of *ammonium chloride solution R* and 1 mL of *dilute ammonia R1*. Heat to boiling. No turbidity or precipitate is formed.

If intended for use in the manufacture of dialysis solutions, the above test is replaced by the following test for aluminium (2.4.17): maximum 1 ppm.

Prescribed solution Dissolve 6 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Iron (2.4.9)

Maximum 7 ppm, determined on solution S.

Magnesium and alkali metals

Maximum 0.3 per cent.

To a mixture of 20 mL of solution S and 80 mL of *water R* add 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*, heat to boiling and pour into the boiling solution a hot solution of 5 g of *ammonium oxalate R* in 75 mL of *water R*. Allow to stand for 4 h, dilute to 200 mL with *water R* and filter through a suitable filter. To 100 mL of the filtrate add 0.5 mL of *sulfuric acid R*. Evaporate to dryness on a water-bath and ignite to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

ASSAY

Dissolve 0.200 g in 100 mL of *water R*. Carry out the complexometric titration of calcium (2.5.11).

1 mL of *0.1 M sodium edetate* is equivalent to 21.91 mg of $CaCl_2,6H_2O$.

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Chloride Injection

General Notices

DEFINITION

Calcium Chloride Injection is a sterile solution of Calcium Chloride Dihydrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of calcium chloride dihydrate, $CaCl_2,2H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. 1 mL yields reaction C characteristic of *calcium salts*, Appendix VI.

B. Dilute 1 volume of the injection to 50 mL with *water*. The resulting solution yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity or alkalinity

pH 5.0 to 8.0, Appendix V L.

Colour of solution

The injection is not more intensely coloured than *reference solution* BY_6, Appendix IV B, Method II.

ASSAY

Carry out the *complexometric titration of calcium*, Appendix VIII D. Use a volume of the injection containing about 0.3 g of Calcium Chloride Dihydrate. Each mL of 0.1M *sodium edetate* is equivalent to 14.70 mg of $CaCl_2,2H_2O$.

LABELLING

The label states (1) the percentage w/v of Calcium Chloride Dihydrate; (2) the concentration of calcium ion as millimoles in a suitable volume; (3) the concentration of chloride ion as millimoles in a suitable volume; (4) that solutions containing visible solid particles must not be used.

When calcium chloride intravenous infusion is prescribed or demanded, Calcium Chloride Injection shall be dispensed or supplied.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

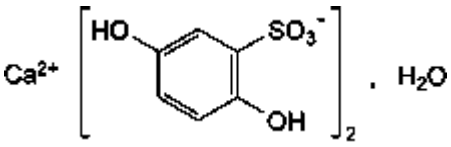
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Dobesilate Monohydrate

General Notices

(Ph. Eur. monograph 1183)



$C_{12}H_{10}CaO_{10}S_2,H_2O$ 436.4 *20123-80-2*

Ph Eur

DEFINITION

Calcium di(2,5-dihydroxybenzenesulfonate) monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Very soluble in water, freely soluble in anhydrous ethanol, very slightly soluble in 2-propanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution Dissolve 0.100 g in *water R* and dilute to 200.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *water R*.

Spectral range 210-350 nm.

Absorption maxima At 221 nm and 301 nm.

Specific absorbance at the absorption maximum at 301 nm 174 to 181.

www.webofpharma.com

https://thuocngocanh.com/

B. Mix 1 mL of *ferric chloride solution R2*, 1 mL of a freshly prepared 10 g/L solution of *potassium ferricyanide R* and 0.1 mL of *nitric acid R*. To this mixture add 5 mL of freshly prepared solution S (see Tests): a blue colour and a precipitate are immediately produced.

C. 2 mL of freshly prepared solution S gives reaction (b) of calcium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S, when freshly prepared, is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

4.5 to 6.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*). *Keep all solutions at 2-8 °C.*

Buffer solution Dissolve 1.2 g of *anhydrous sodium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, adjust to pH 6.5 with *disodium hydrogen phosphate solution R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 10 mg of the substance to be examined and 10 mg of *hydroquinone R* (impurity A) in *water R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 100 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R1*, buffer solution (10:90 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time 2.5 times the retention time of dobesilate.

Relative retention With reference to dobesilate (retention time = about 6 min): impurity A = about 1.7.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (b):

— *resolution*: minimum 8.0 between the peaks due to dobesilate and impurity A.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.6;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Iron (*2.4.9*)

Maximum 10 ppm, determined on 10 mL of solution S.

Water (*2.5.12*)

4.0 per cent to 6.0 per cent, determined on 0.500 g.

ASSAY

Dissolve 0.200 g in a mixture of 10 mL of *water R* and 40 mL of *dilute sulfuric acid R*. Titrate with *0.1 M cerium sulfate*, determining the end-point potentiometrically (*2.2.20*).

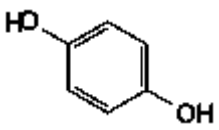
1 mL of *0.1 M cerium sulfate* is equivalent to 10.45 mg of $C_{12}H_{10}CaO_{10}S_2$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A.*



A. benzene-1,4-diol (hydroquinone).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

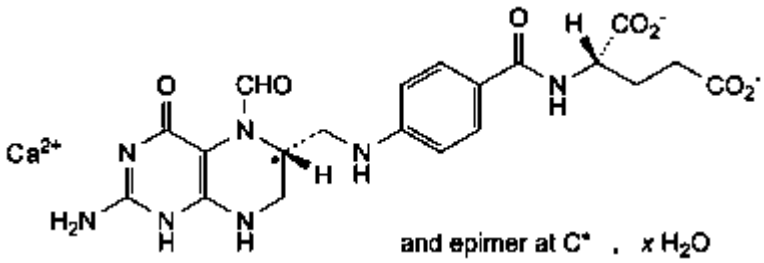
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Folinate Hydrate

General Notices

Calcium Folinate

(Ph. Eur. monograph 0978)



$C_{20}H_{21}CaN_7O_7,xH_2O$ 511.5 (anhydrous substance) *2060570-47-8*

Action and use

Antidote to folic acid antagonists.

Preparations

Calcium Folinate Injection

Calcium Folinate Tablets

Ph Eur

DEFINITION

Calcium (2*S*)-2-[4-[[[(6*RS*)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzamido]pentanedioate hydrate.

Content

— *calcium folinate* ($C_{20}H_{21}CaN_7O_7$): 97.0 per cent to 102.0 per cent (anhydrous substance);

— *calcium* (Ca; A_r 40.08): 7.54 per cent to 8.14 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or light yellow, amorphous or crystalline, hygroscopic powder.

Solubility

Sparingly soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

The amorphous form may produce supersaturated solutions in water.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B, D.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *calcium folinate CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *water R* and add dropwise sufficient *acetone R* to produce a precipitate. Allow to stand for 15 min, collect the precipitate by centrifugation, wash the precipitate with 2 small quantities of *acetone R* and dry. Record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 15 mg of the substance to be examined in a 3 per cent *V/V* solution of *ammonia R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 15 mg of *calcium folinate CRS* in a 3 per cent *V/V* solution of *ammonia R* and dilute to 5 mL with the same solvent.

Plate *cellulose for chromatography F_{254} R* as the coating substance.

Mobile phase The lower layer of a mixture of 1 volume of *isoamyl alcohol R* and 10 volumes of a 50 g/L solution of *citric acid monohydrate R* previously adjusted to pH 8 with *ammonia R*.

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

www.webofpharma.com

https://thuocngocanh.com/

D. It gives reaction (b) of calcium (2.3.1).

TESTS

Carry out the tests as rapidly as possible, protected from actinic light.

Solution S

Dissolve 1.25 g in *carbon dioxide-free water R*, heating at 40 °C if necessary, and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1).

pH (2.2.3)

6.8 to 8.0 for solution S.

Specific optical rotation (2.2.7)

+ 14.4 to + 18.0 (anhydrous substance), determined on solution S.

Absorbance (2.2.25)

Maximum 0.60, determined at 420 nm on solution S.

Ethanol

Head-space gas chromatography (2.2.28): use the standard additions method.

Test solution Dissolve 0.25 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dilute 0.750 g of *anhydrous ethanol R* to 1000.0 mL with *water R*.

Column:

— *material*: fused silica;

— *size*: *l* = 10 m, Ø = 0.32 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 4 mL/min.

Static head-space conditions that may be used:

— *equilibration temperature*: 80 °C;

www.webofpharma.com

https://thuocngocanh.com/

— *equilibration time*: 20 min;

— *pressurisation time*: 30 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	125 → 185
	6 - 15	185
Injection port		250
Detector		250

Detection Flame ionisation.

Injection At least 3 times.

Limit:

— *ethanol*: maximum 3.0 per cent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 10.0 mg of the substance to be examined in water R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of calcium folinate CRS in water R and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with water R. Dilute 1.0 mL of this solution to 10.0 mL with water R.

Reference solution (c) Dissolve 5 mg of calcium folinate for system suitability CRS (containing impurities A, E and F) in 5 mL of water R.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 165 mL of methanol R and 835 mL of a solution containing 4.0 mL of tetrabutylammonium dihydrogen phosphate solution R and 1.42 g of disodium hydrogen phosphate dihydrate R in water for chromatography R, previously adjusted to pH 7.7 with phosphoric acid R or dilute sodium hydroxide solution R.

Flow rate 1.25 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time 3.5 times the retention time of folinic acid.

Identification of impurities Use the chromatogram supplied with *calcium folinate for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, E and F.

Relative retention With reference to folinic acid (retention time = about 13.9 min): impurity E = about 0.4; impurity A = about 0.6; impurity F = about 0.7.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to impurities A and F.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity E = 0.6; impurity F = 0.6;

— for each impurity, use the concentration of calcium folinate hydrate in reference solution (b).

Limits:

— *impurities A, E, F*: for each impurity, maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.20 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides

Maximum 0.5 per cent.

Dissolve 0.300 g in 50 mL of *water R* heating at 40 °C if necessary. Add 10 mL of *dilute nitric acid R* and titrate with *0.005 M silver nitrate* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.005 M silver nitrate* is equivalent to 0.177 mg of Cl.

Water

(*2.5.12*): 10.0 per cent to 17.0 per cent.

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.100 g in a mixture of 15 mL of *formamide R* and 50 mL of the titration solvent. Stir for about 6 min before titrating and use a suitable titrant that does not contain pyridine.

ASSAY

Carry out the assays as rapidly as possible, protected from actinic light.

Calcium

Dissolve 0.400 g in 150 mL of *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 4.008 mg of Ca.

Calcium folinate

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{20}H_{21}CaN_7O_7$ taking into account the assigned content of *calcium folinate CRS*.

STORAGE

In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

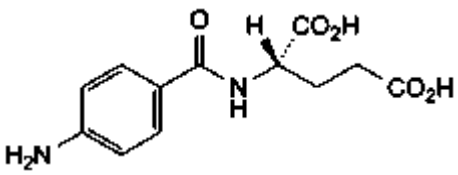
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities *A, E, F.*

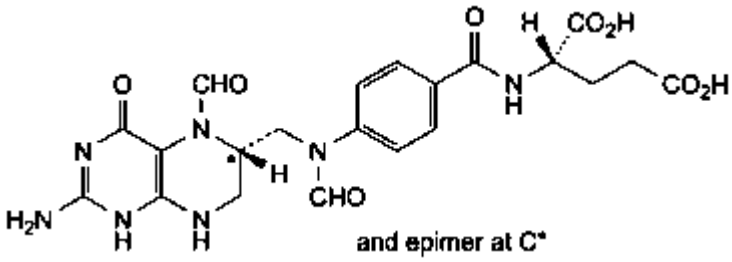
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, G, I.*



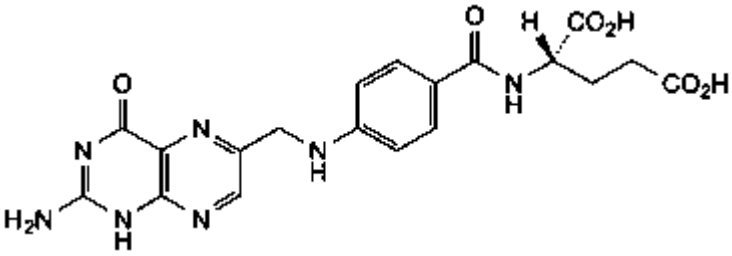
A. (2*S*)-2-(4-aminobenzamido)pentanedioic acid,

www.webofpharma.com

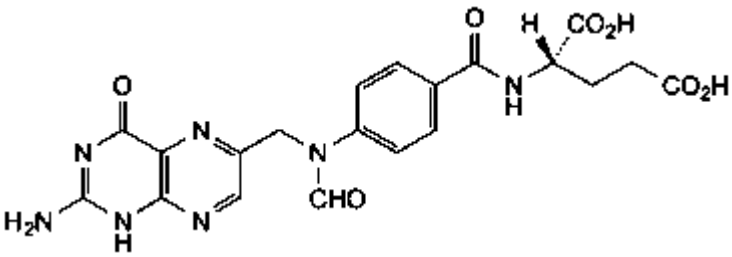
https://thuocngocanh.com/



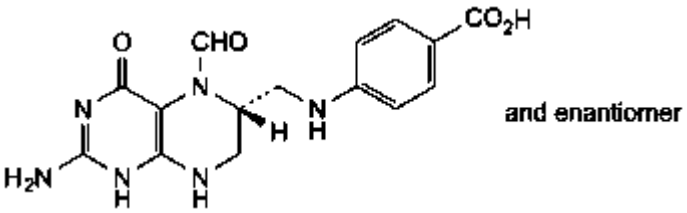
B. (2*S*)-2-[4-[[[(6*RS*)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl](formyl)amino]benzamido]pentanedioic acid (5,10-diformyltetrahydrofolic acid),



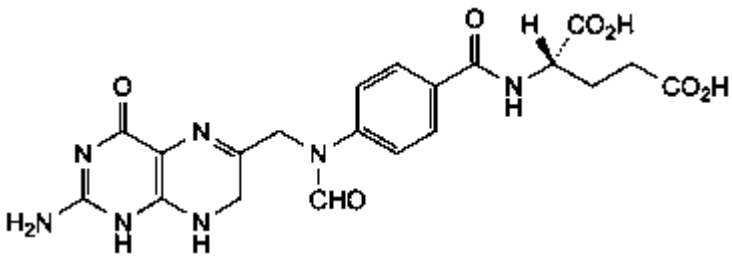
C. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino]benzamido]pentanedioic acid (folic acid),



D. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl](formyl)amino]benzamido]pentanedioic acid (10-formylfolic acid),



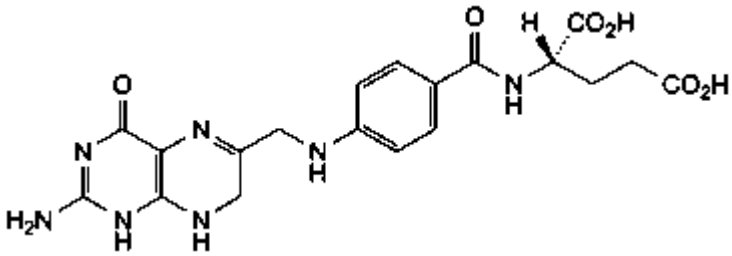
E. 4-[[[(6*RS*)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzoic acid (5-formyltetrahydropteroic acid),



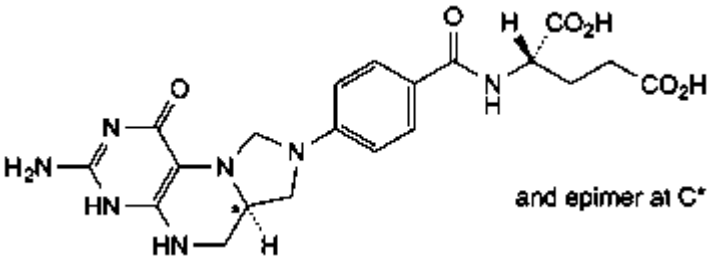
F. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4,7,8-tetrahydropteridin-6-yl)methyl](formyl)amino]benzamido]pentanedioic acid (10-formyldihydrofolic acid),

www.webofpharma.com

https://thuocngocanh.com/



G. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4,7,8-tetrahydropteridin-6-yl)methyl]amino]benzamido]pentanedioic acid (dihydrofolic acid),



I. (2*S*)-2-[4-[(6a*RS*)-3-amino-1-oxo-1,2,5,6,6a,7-hexahydroimidazo[1,5-*f*]pteridin-8(9*H*)-yl]benzamido]pentanedioic acid ((6a*RS*)-5,10-methylenetetrahydrofolic acid).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Folinate Injection

General Notices

Action and use

Vitamin B component.

DEFINITION

Calcium Folinate Injection is a sterile solution of Calcium Folinate Hydrate. It is either supplied as a ready-to-use solution or it is prepared by dissolving Calcium Folinate for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations and, when supplied as a ready-to-use solution, with the following requirements.

Content of folinic acid, $C_{20}H_{23}N_7O_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a volume containing the equivalent of 20 mg of folinic acid add 40 mL of *acetone*, mix, allow to stand and then centrifuge, discarding the solvent. Suspend the residue in 40 mL of *acetone* and centrifuge. Dry the residue in a stream of nitrogen and then at a pressure of 0.7 kPa for 2 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of calcium folinate *(RS 368)*.

B. Yields reaction B characteristic of *calcium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH, 6.5 to 8.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Dilute with *water*, if necessary, a volume of the injection to produce a solution containing the equivalent of 0.1% w/v of folinic acid.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(3) 0.1% w/v of *calcium folinate BPCRS* in *water*.

(4) Dilute 1 volume of solution (2) to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 2.5 times the retention time of folinate.

MOBILE PHASE

220 mL of *methanol* and 780 mL of a solution containing 2.0 mL of *tetrabutylammonium hydroxide solution* and 2.2 g of *disodium hydrogen orthophosphate*, previously adjusted to pH 7.5 with 10% v/v *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention times of calcium folinate and formyl folic acid are about 12 minutes and 21 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to folinate and formylfolic acid is at least 2.2. If necessary, adjust the methanol content in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to formylfolic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks*, excluding the peak corresponding to formylfolic acid, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Protect the solutions from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection with *water* to produce a solution containing the equivalent of 0.01% w/v of folinic acid.

(2) 0.011% w/v of *calcium folinate BPCRS* in *water*.

(3) 0.1% w/v of *calcium folinate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to folinate and formylfolic acid is at least 2.2. If necessary, adjust the methanol content in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{23}N_7O_7$ in the injection using the declared content of $C_{20}H_{21}CaN_7O_7$ in *calcium folinate BPCRS*. Each mg of $C_{20}H_{21}CaN_7O_7$ is equivalent to 0.9255 mg of $C_{20}H_{23}N_7O_7$.

STORAGE

When supplied as a ready-to-use solution, Calcium Folinate Injection should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of folinic acid.

CALCIUM FOLINATE FOR INJECTION

DEFINITION

Calcium Folinate for Injection is a sterile material consisting of Calcium Folinate Hydrate with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of folinic acid, $C_{20}H_{23}N_7O_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of calcium folinate *(RS 368)*. If the spectra are not concordant prepare a solution containing 1% w/v of Calcium Folinate and carry out Identification Test A for the ready-to-use solution.

B. Yield reaction B characteristic of *calcium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 1.0% w/v of folinic acid, 6.5 to 8.5, Appendix V L.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Carry out the test described for the ready-to-use solution but using the following solution as solution (1). Dissolve sufficient of the mixed contents of 10 containers in *water* to produce a solution containing the equivalent of 0.1% w/v of folinic acid.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Carry out the Assay described for the ready-to-use solution but using the following solution as solution (1). Dissolve sufficient of the mixed contents of the 10 containers in *water* to produce a solution containing the equivalent of 0.01% w/v of folinic acid.

Calculate the content of $C_{20}H_{23}N_7O$ in a container of average content weight using the declared content of $C_{20}H_{21}CaN_7O_7$ in *calcium folinate BPCRS*. Each mg of $C_{20}H_{21}CaN_7O_7$ is equivalent to 0.9255 mg of $C_{20}H_{23}N_7O_7$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of folinic acid.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Folinate Tablets

General Notices

Action and use

Vitamin B component.

DEFINITION

Calcium Folinate Tablets contain Calcium Folinate Hydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of folinic acid, $C_{20}H_{23}N_7O_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing the equivalent of 180 mg of folinic acid add 10 mL of *water*, mix with the aid of ultrasound, and filter. Add 125 mg of *ammonium oxalate* to the filtrate, shake, and centrifuge until a clear supernatant liquid is obtained. To the supernatant add 1 mL of *methanol* and 3 drops of *hydrochloric acid*, and shake. If the preparation is cloudy, add *methanol* until a clear solution is obtained and filter, if necessary, to remove any undissolved material. Cool the preparation at 0° until a precipitate forms and centrifuge. The cooling and centrifuging steps may be repeated, if necessary, to increase the amount of precipitate collected. Decant the supernatant liquid and dissolve the precipitate in 2 mL of *methanol*. Evaporate to dryness under a current of air and dry the residue at 50° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of calcium folinate *(RS 368)*.

B. The powdered tablets yield reaction B characteristic of *calcium salts*, Appendix VI.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Add 20 mL of *water* to a quantity of the powdered tablets containing the equivalent of 25 mg of folinic acid, shake for 15 minutes and dilute to 25 mL with *water*. Filter through a glass fibre filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(3) 0.1% w/v of *calcium folinate BPCRS* in *water*.

(4) Dilute 1 volume of solution (2) to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 2.5 times the retention time of folinate.

MOBILE PHASE

220 mL of *methanol* and 780 mL of a solution containing 2.0 mL of *tetrabutylammonium hydroxide solution* and 2.2 g of *disodium hydrogen orthophosphate*, previously adjusted to pH 7.5 with 10% v/v *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to folinate and formylfolic acid is at least 2.2. If necessary, adjust the methanol content in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to formylfolic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks*, excluding the peak corresponding to formylfolic acid, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Protect the solutions from light. Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 200 mL of *water* to a quantity of the powdered tablets containing the equivalent of 25 mg of folinic acid, shake for 15 minutes and dilute to 250 mL with *water*. Filter through a glass fibre filter (Whatman GF/C is suitable).

(2) 0.011% w/v of *calcium folinate BPCRS* in *water*.

(3) 0.1% w/v of *calcium folinate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to folinate and formylfolic acid is at least 2.2. If necessary, adjust the methanol content in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{23}N_7O_7$ in the tablets using the declared content of $C_{20}H_{21}CaN_7O_7$ in *calcium folinate BPCRS*. Each mg of $C_{20}H_{21}CaN_7O_7$ is equivalent to 0.9255 mg of $C_{20}H_{23}N_7O_7$.

STORAGE

Calcium Folinate Tablets should be stored at a temperature not exceeding 30°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of folinic acid.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

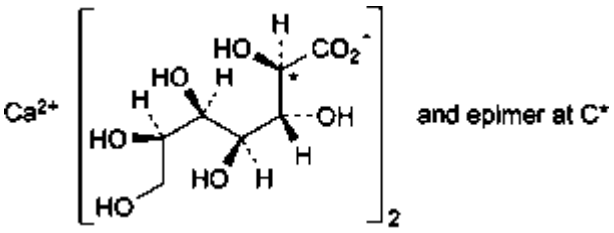
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Calcium Glucoheptonate

General Notices

(Ph. Eur. monograph 1399)



$C_{14}H_{26}CaO_{16}$ 490.4

Action and use

Used in treatment of calcium deficiency.

Ph Eur

DEFINITION

Mixture in variable proportions, of calcium di(D-*glycero*-D-*gulo*-heptonate) and calcium di(D-*glycero*-D-*ido*-heptonate).

Content

98.0 per cent to 102.0 per cent of calcium 2,3,4,5,6,7-hexahydroxyheptanoate (dried substance).

CHARACTERS

Appearance

White or very slightly yellow, amorphous powder, hygroscopic.

Solubility

Very soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of *water R*.

Reference solution (a) Dissolve 20 mg of *calcium glucoheptonate CRS* in 1 mL of *water R*.

Reference solution (b) Dissolve 10 mg of *calcium gluconate CRS* in 0.5 mL of the test solution and dilute to 1 mL with *water R*.

Plate *cellulose for chromatography R1* as the coating substance.

Mobile phase *formic acid R*, *water R*, *acetone R*, *butanol R* (20:20:30:30 *V/V/V/V*); use a freshly prepared mixture.

Application 10 µL as bands of 20 mm by 2 mm.

Development In a tank previously allowed to saturate for 10 min, over a path of 12 cm.

Drying In air.

Detection Spray with *0.02 M potassium permanganate*.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

B. 0.2 mL of solution S (see Tests) gives reaction (b) of calcium (*2.3.1*).

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*)

6.0 to 8.0 for solution S.

Reducing sugars

Maximum 1 per cent, expressed as glucose.

Dissolve 1.0 g in 5 mL of *water R* with the aid of gentle heat. Cool and add 20 mL of *cupri-citric solution R* and a few glass beads. Heat so that boiling begins after 4 min and maintain boiling for 3 min. Cool rapidly and add 100 mL of a 2.4 per cent *V/V* solution of *glacial acetic acid R* and 20.0 mL of *0.025 M iodine*. With continuous shaking, add 25 mL of a mixture of 6 volumes of *hydrochloric acid R* and

www.webofpharma.com

https://thuocngocanh.com/

94 volumes of *water R* until the precipitate dissolves, titrate the excess of iodine with *0.05 M sodium thiosulfate* using 1 mL of *starch solution R* added towards the end of the titration, as indicator. Not less than 12.6 mL of *0.05 M sodium thiosulfate* is required.

Cyanide

Dissolve 5.0 g in 50 mL of *water R* and add 2.0 g of *tartaric acid R*. Place this solution in a distillation apparatus (*2.2.11*). The plain bend adapter attached to the end of the condenser has a vertical part that is long enough to extend to 1 cm from the bottom of a 50 mL test-tube used as a receiver. Place 10 mL of *water R* and 2 mL of *0.1 M sodium hydroxide* into the receiver. Distil, collect 25 mL of distillate and dilute to 50 mL with *water R*. To 25 mL of this solution add 25 mg of *ferrous sulfate R* and boil for a short time. After cooling to about 70 °C add 10 mL of *hydrochloric acid R1*. After 30 min, filter the solution and wash the filter. A yellow spot appears on the filter; there is no blue or green spot.

Chlorides (*2.4.4*)

Maximum 100 ppm.

To 5 mL of solution S, add 10 mL of *water R*.

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Iron (*2.4.9*)

Maximum 40 ppm.

Dilute 2.5 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Bacterial endotoxins (*2.6.14*)

Less than 167 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 0.800 g in a mixture of 2 mL of *3 M hydrochloric acid R* and 150 mL of *water R*. While stirring, add 12.5 mL of *0.1 M sodium edetate*, 15 mL of *1 M sodium hydroxide* and 0.3 g of *hydroxynaphthol blue, sodium salt R*. Titrate with *0.1 M sodium edetate* until the colour changes from violet to pure blue.

1 mL of *0.1 M sodium edetate* is equivalent to 49.04 mg of $C_{14}H_{26}CaO_{16}$.

STORAGE

In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

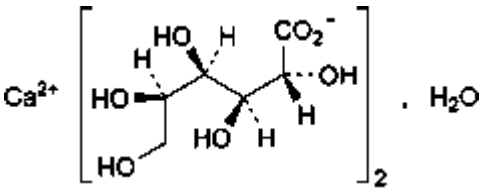
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Gluconate

General Notices

(Ph. Eur. monograph 0172)



$C_{12}H_{22}CaO_{14},H_2O$ 448.4 *18016-24-5*

Action and use

Used in treatment of calcium deficiency.

Preparations

Calcium Gluconate Tablets

Calcium Gluconate Chewable Tablets

Calcium Gluconate Effervescent Tablets

Ph Eur

DEFINITION

Calcium bis[(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate] monohydrate (calcium di(D-gluconate) monohydrate).

Content

98.5 per cent to 102.0 per cent of $C_{12}H_{22}CaO_{14},H_2O$.

CHARACTERS

Appearance

White or almost white, crystalline or granular powder.

Solubility

Sparingly soluble in water, freely soluble in boiling water.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of water R, heating if necessary in a water-bath at 60 °C.

Reference solution Dissolve 20 mg of calcium gluconate CRS in 1 mL of water R, heating if necessary in a water-bath at 60 °C.

Plate TLC silica gel plate R (5-40 µm) [or TLC silica gel plate R (2-10 µm)].

Mobile phase concentrated ammonia R, ethyl acetate R, water R, ethanol (96 per cent) R (10:10:30:50 *V/V/V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying At 100 °C for 20 min; allow to cool.

Detection Spray with a solution containing 10 g/L of cerium sulfate R and 25 g/L of ammonium molybdate R in dilute sulfuric acid R and heat at 105 °C for about 10 min.

Results After 5 min, the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Solution S (see Tests) gives reaction (b) of calcium (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in water R heated to 60 °C and dilute to 50 mL with the same solvent.

Appearance of solution

At 60 °C, solution S is not more intensely coloured than reference solution Y_6 (2.2.2, Method II). After cooling, it is not more opalescent than reference suspension II (2.2.1).

Organic impurities and boric acid

Introduce 0.5 g into a porcelain dish previously rinsed with sulfuric acid R and placed in a bath of iced water. Add 2 mL of cooled sulfuric acid R and mix. No yellow or brown colour develops. Add 1 mL of chromotrope II B solution R. A violet colour develops and does not become dark blue. The solution is not more intensely coloured than that of a mixture of 1 mL of chromotrope II B solution R and 2 mL of cooled sulfuric acid R.

Sucrose and reducing sugars

Dissolve 0.5 g in a mixture of 2 mL of hydrochloric acid R1 and 10 mL of water R. Boil for 5 min, allow to cool, add 10 mL of sodium carbonate solution R and allow to stand. Dilute to 25 mL with water R and filter. To 5 mL of the filtrate add 2 mL of cupri-tartaric solution R

www.webofpharma.com

https://thuocngocanh.com/

and boil for 1 min. Allow to stand for 2 min. No red precipitate is formed.

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 12.5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 100 ppm.

Dissolve 10.0 g with heating in a mixture of 10 mL of *acetic acid R* and 90 mL of *distilled water R*.

Magnesium and alkali metals

Maximum 0.4 per cent.

Dissolve 1.00 g in 100 mL of boiling *water R*, add 10 mL of *ammonium chloride solution R*, 1 mL of *ammonia R* and, dropwise, 50 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 200 mL with *water R* and filter. Evaporate 100 mL of the filtrate to dryness and ignite. The residue weighs a maximum of 2 mg.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (2.6.12).

TYMC: acceptance criterion 10^2 CFU/g (2.6.12).

ASSAY

Dissolve 0.8000 g in 20 mL of hot *water R*, allow to cool and dilute to 300 mL with *water R*. Carry out the complexometric titration of calcium (2.5.11).

1 mL of *0.1 M sodium edetate* is equivalent to 44.84 mg of $C_{12}H_{22}CaO_{14},H_2O$.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Gluconate Chewable Tablets

General Notices

Chewable Calcium Gluconate Tablets

DEFINITION

Calcium Gluconate Chewable Tablets contain Calcium Gluconate in a Chocolate Basis or other suitable basis with a chocolate flavour.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of calcium gluconate, $C_{12}H_{22}CaO_{14},H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract five tablets, finely powdered, with two 25-mL quantities of *petroleum spirit (boiling range, 40° to 60°)*, discard the extracts and repeat the extraction with three 10-mL quantities of *water*, again discarding the extracts. Dissolve the residue as completely as possible in 30 mL of hot *water*, filter and to 0.5 mL of the filtrate add 0.05 mL of *iron(III) chloride solution R1*. An intense yellow colour is produced.

B. To a volume of the filtrate obtained in test A containing 0.5 g of Calcium Gluconate add 0.65 mL of *glacial acetic acid* and 1 mL of *phenylhydrazine*, heat on a water bath for 30 minutes, cool and induce crystallisation. Filter, dissolve the residue in 10 mL of hot *water*, add a few mg of *activated charcoal*, shake, filter, allow the filtrate to cool and induce crystallisation. A white, crystalline precipitate is produced. The *melting point* of the crystals, after drying, is about 201°, with decomposition, Appendix V A.

C. The powdered tablets yield the reactions characteristic of *calcium salts*, Appendix VI.

TESTS

Disintegration

The requirement for Disintegration does not apply to Calcium Gluconate Chewable Tablets.

ASSAY

Weigh and powder 20 tablets. Ignite a quantity of the powder containing 0.5 g of Calcium Gluconate, cool and dissolve the residue with gentle heat in 5 mL of 2M *hydrochloric acid*. Filter, wash the residue on the filter with *water* and dilute the combined filtrate and washings to 50 mL with *water*. Neutralise with 5M *ammonia*, using *methyl orange solution* as indicator, add 5 mL of 8M *sodium hydroxide* and titrate with 0.05M *disodium edetate VS* using *calconcarboxylic acid triturate* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 22.42 mg of $C_{12}H_{22}CaO_{14},H_2O$.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Gluconate Effervescent Tablets

General Notices

Effervescent Calcium Gluconate Tablets

DEFINITION

Calcium Gluconate Effervescent Tablets contain Calcium Gluconate in a suitable effervescent basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of calcium gluconate, $C_{12}H_{22}CaO_{14},H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powdered tablets containing 1 g of Calcium Gluconate in 20 mL of hot *water*, cool and filter. To 0.5 mL of the filtrate add 0.05 mL of *iron(III) chloride solution R1*. An intense yellow colour is produced.

B. To 5 mL of the filtrate obtained in test A add 0.65 mL of *glacial acetic acid* and 1 mL of *phenylhydrazine*, heat on a water bath for 30 minutes, allow to cool and induce crystallisation. Filter, dissolve the residue in 10 mL of hot *water*, add a suitable quantity of *activated charcoal*, shake, filter, allow the filtrate to cool and induce crystallisation. A white, crystalline precipitate is produced. The *melting point* of the crystals, after drying, is about 201°, with decomposition, Appendix V A.

C. The powdered tablets yield reaction B characteristic of *calcium salts*, Appendix VI.

D. The tablets effervesce on the addition of *water*.

ASSAY

Weigh and powder 20 tablets. Ignite a quantity of the powder containing 0.5 g of Calcium Gluconate, cool and dissolve the residue with gentle heat in 5 mL of 2M *hydrochloric acid*. Filter, wash the residue on the filter with *water* and dilute the combined filtrate and washings to 50 mL with *water*. Neutralise with 5M *ammonia*, using *methyl orange solution* as indicator, add 5 mL of 8M *sodium hydroxide* and titrate with 0.05M *disodium edetate VS* using *calconcarboxylic acid triturate* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 22.42 mg of $C_{12}H_{22}CaO_{14},H_2O$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

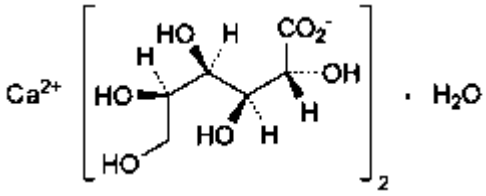
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Gluconate for Injection

General Notices

(Ph. Eur. monograph 0979)



$C_{12}H_{22}CaO_{14},H_2O$ 448.4 *18016-24-5*

Action and use

Used in treatment of calcium deficiency.

Preparation

Calcium Gluconate Injection

Ph Eur

DEFINITION

Calcium bis[(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate] monohydrate (calcium di(D-gluconate) monohydrate).

Content

99.0 per cent to 101.0 per cent of $C_{12}H_{22}CaO_{14},H_2O$.

CHARACTERS

Appearance

White or almost white, crystalline or granular powder.

Solubility

Sparingly soluble in water, freely soluble in boiling water.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of *water R*, heating if necessary in a water-bath at 60 °C.

Reference solution Dissolve 20 mg of *calcium gluconate CRS* in 1 mL of *water R*, heating if necessary in a water-bath at 60 °C.

Plate *TLC silica gel plate R* (5-40 µm) [or *TLC silica gel plate R* (2-10 µm)].

Mobile phase *concentrated ammonia R*, *ethyl acetate R*, *water R*, *ethanol (96 per cent) R* (10:10:30:50 *V/V/V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying At 100 °C for 20 min; allow to cool.

Detection Spray with a solution containing 10 g/L of *cerium sulfate R* and 25 g/L of *ammonium molybdate R* in *dilute sulfuric acid R* and heat at 105 °C for about 10 min.

Results After 5 min, the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. About 20 mg gives reaction (b) of calcium (*2.3.1*).

TESTS

Solution S

To 10.0 g add 90 mL of boiling *distilled water R* and boil with stirring, for not more than 10 s, until completely dissolved, then dilute to 100.0 mL with the same solvent.

Appearance of solution

At 60 °C, solution S is not more intensely coloured than reference solution B_7 (*2.2.2, Method II*). After cooling to 20 °C, it is not more opalescent than reference suspension II (*2.2.1*).

pH (*2.2.3*)

6.4 to 8.3.

Dissolve 1.0 g in 20 mL of *carbon dioxide-free water R*, heating on a water-bath.

Organic impurities and boric acid

Introduce 0.5 g into a porcelain dish previously rinsed with *sulfuric acid R* and placed in a bath of iced water. Add 2 mL of cooled *sulfuric acid R* and mix. No yellow or brown colour develops. Add 1 mL of *chromotrope II B solution R*. A violet colour develops and does not become dark blue. The solution is not more intensely coloured than that of a mixture of 1 mL of *chromotrope II B solution R* and 2 mL of cooled *sulfuric acid R*.

Oxalates

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Solvent mixture Dilute 1 mL of hydrochloric acid R to 1200 mL with water for chromatography R.

Test solution Dissolve 0.200 g of the substance to be examined in the solvent mixture using sonication and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 2.0 mL of a 0.152 g/L solution of sodium oxalate R to 100.0 mL with the solvent mixture.

Reference solution (b) Mix 2 mL of a 0.152 g/L solution of sodium oxalate R, 20 mL of sulfate standard solution (10 ppm SO_4) R and 50 mL of water for chromatography R, and dilute to 100 mL with water for chromatography R.

Precolumn:

— *size*: *l* = 50 mm, Ø = 4 mm;

— *stationary phase*: strongly basic anion-exchange resin for chromatography R2 (13 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: strongly basic anion-exchange resin for chromatography R2 (13 µm).

Mobile phase Dissolve 0.143 g of sodium hydrogen carbonate R and 0.191 g of anhydrous sodium carbonate R in water for chromatography R and dilute to 1000 mL with the same solvent.

Flow rate 2 mL/min.

Detection Conductivity detector equipped with a suitable ion suppressor.

Injection 50 µL.

Run time 1.5 times the retention time of oxalate.

Retention time Sulfate = about 8.1 min; oxalate = about 10.6 min.

System suitability Reference solution (b):

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the area of the peak due to oxalate, determined on 5 injections;

— *resolution*: minimum 4.0 between the peaks due to sulfate and oxalate.

Calculation of content:

— for oxalates, use the concentration of sodium oxalate in reference solution (a).

Limit:

— *oxalates*: maximum 100 ppm.

www.webofpharma.com

https://thuocngocanh.com/

Sucrose and reducing sugars

Dissolve 0.5 g in a mixture of 2 mL of *hydrochloric acid R1* and 10 mL of *water R*. Boil for 5 min, allow to cool, add 10 mL of *sodium carbonate solution R* and allow to stand for 10 min. Dilute to 25 mL with *water R* and filter. To 5 mL of the filtrate add 2 mL of *cupri-tartaric solution R* and boil for 1 min. Allow to stand for 2 min. No red precipitate is formed.

Chlorides (*2.4.4*)

Maximum 50 ppm.

To 10 mL of previously filtered solution S add 5 mL of *water R*.

Phosphates (*2.4.11*)

Maximum 100 ppm.

Dilute 1 mL of solution S to 100 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 50 ppm, determined on previously filtered solution S.

Prepare the standard using a mixture of 7.5 mL of *sulfate standard solution (10 ppm SO_4) R* and 7.5 mL of *distilled water R*.

Iron

Maximum 5 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Introduce 2.0 g into a 100 mL polytetrafluoroethylene beaker and add 5 mL of *nitric acid R*. Boil, evaporating almost to dryness. Add 1 mL of *strong hydrogen peroxide solution R* and evaporate again almost to dryness. Repeat the hydrogen peroxide treatment until a clear solution is obtained. Using 2 mL of *nitric acid R*, transfer the solution into a 25 mL volumetric flask. Dilute to 25.0 mL with *dilute hydrochloric acid R*. In the same manner, prepare a compensation solution using 0.65 g of *calcium chloride R1* instead of the substance to be examined.

Reference solutions Prepare the reference solutions from *iron standard solution (20 ppm Fe) R*, diluting with *dilute hydrochloric acid R*.

Source Iron hollow-cathode lamp.

Wavelength 248.3 nm.

Atomisation device Air-acetylene flame.

Carry out a basic correction using a deuterium lamp.

Magnesium and alkali metals

Maximum 0.4 per cent.

www.webofpharma.com

https://thuocngocanh.com/

To 0.50 g add a mixture of 1.0 mL of *dilute acetic acid R* and 10.0 mL of *water R* and rapidly boil, whilst shaking, until completely dissolved. To the boiling solution add 5.0 mL of *ammonium oxalate solution R* and allow to stand for at least 6 h. Filter through a sintered-glass filter (1.6) (*2.1.2*) into a porcelain crucible. Carefully evaporate the filtrate to dryness and ignite. The residue weighs not more than 2 mg.

Bacterial endotoxins (*2.6.14*)

Less than 167 IU/g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

ASSAY

Dissolve 0.350 g in 20 mL of hot *water R*, allow to cool and dilute to 300 mL with *water R*. Carry out the complexometric titration of calcium (*2.5.11*). Use 50 mg of *calconecarboxylic acid triturate R*.

1 mL of *0.1 M sodium edetate* is equivalent to 44.84 mg of $C_{12}H_{22}CaO_{14},H_2O$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Gluconate Injection

General Notices

DEFINITION

Calcium Gluconate Injection is a sterile solution of Calcium Gluconate for Injection in Water for Injections. Not more than 5.0% of the Calcium Gluconate may be replaced with calcium M-saccharate, or other suitable calcium salt, as a stabilising agent.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of calcium, Ca

8.5 to 9.4% of the content of Calcium Gluconate stated on the label.

IDENTIFICATION

A. To 1 mL add 0.05 mL of *iron(III) chloride solution R1*. An intense yellow colour is produced.

B. Warm a volume containing the equivalent of 0.5 g of Calcium Gluconate, add 0.65 mL of *glacial acetic acid* and 1 mL of *phenylhydrazine*. Heat on a water bath for 30 minutes, allow to cool and induce crystallisation. Filter, dissolve the residue in 10 mL of hot *water*, add a few mg of *activated charcoal*, shake, filter, allow the filtrate to cool and induce crystallisation. A white, crystalline precipitate is produced. The *melting point* of the crystals, after drying, is about 200°, with decomposition, Appendix V A.

C. Yields the reactions characteristic of *calcium salts*, Appendix VI.

TESTS

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection in *water BET* if necessary to give a solution containing 100 mg of Calcium Gluconate per millilitre (solution A). The endotoxin limit concentration of solution A is 16.7 IU per mL.

ASSAY

To a volume containing the equivalent of 0.5 g of Calcium Gluconate add 300 mL of *water* and carry out the *complexometric titration of calcium*, Appendix VIII D, beginning at the words ‘add 6 mL of ...’.

LABELLING

The label states (1) the percentage w/v of Calcium Gluconate equivalent to the total amount of calcium present; (2) that solutions containing visible solid particles must not be used; (3) the name and the percentage of any added stabilising agent.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thatuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Gluconate Tablets

General Notices

DEFINITION

Calcium Gluconate Tablets contain Calcium Gluconate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of calcium gluconate, $C_{12}H_{22}CaO_{14},H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract five tablets, finely powdered, with two 25-mL quantities of *petroleum spirit (boiling range, 40° to 60°)*, discard the extracts and repeat the extraction with three 10-mL quantities of *water*, again discarding the extracts. Dissolve the residue as completely as possible in 30 mL of hot *water*, filter and to 0.5 mL of the filtrate add 0.05 mL of *iron(III) chloride solution R1*. An intense yellow colour is produced.

B. To a volume of the filtrate obtained in test A containing 0.5 g of Calcium Gluconate add 0.65 mL of *glacial acetic acid* and 1 mL of *phenylhydrazine*, heat on a water bath for 30 minutes, cool and induce crystallisation. Filter, dissolve the residue in 10 mL of hot *water*, add a few mg of *activated charcoal*, shake, filter, allow the filtrate to cool and induce crystallisation. A white, crystalline precipitate is produced. The *melting point* of the crystals, after drying, is about 201°, with decomposition, Appendix V A.

C. The powdered tablets yield the reactions characteristic of *calcium salts*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *water* and rotate the paddle at 50 revolutions per minute. Withdraw a sample of 20 mL of the medium and filter. Carry out the method for *atomic absorption spectrophotometry*, Appendix II D, measuring at 422.7 nm using a calcium hollow-cathode lamp as the radiation source, an air-acetylene flame and the following solutions.

Test solution Use the filtered dissolution medium diluted, if necessary, with *water* to give a concentration suitable for the instrument used.

Standard solutions Use *calcium standard solution (100 ppm Ca)* suitably diluted with *water*.

Determine the total content of calcium in the dissolution medium and calculate the total content of calcium gluconate taking each mg of calcium to be equivalent to 11.21 mg of $C_{12}H_{22}CaO_{14},H_2O$.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Weigh and powder 20 tablets. Ignite a quantity of the powder containing 0.5 g of Calcium Gluconate, cool and dissolve the residue with gentle heat in 5 mL of 2M *hydrochloric acid*. Filter, wash the residue on the filter with *water* and dilute the combined filtrate and washings to 50 mL with *water*. Neutralise with 5M *ammonia*, using *methyl orange solution* as indicator, add 5 mL of 8M *sodium hydroxide* and titrate with 0.05M *disodium edetate VS* using *calconcarboxylic acid triturate* as indicator. Each mL of 0.05M *disodium edetate VS* is equivalent to 22.42 mg of $C_{12}H_{22}CaO_{14},H_2O$.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Glycerophosphate

General Notices

(Ph. Eur. monograph 0980)

$C_3H_7CaO_6P$ 210.1

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture in variable proportions of the calcium salt of (*RS*)-2,3-dihydroxypropyl phosphate and of 2-hydroxy-1-(hydroxymethyl)ethyl phosphate which may be hydrated.

Content

18.6 per cent to 19.4 per cent of Ca (dried substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Mix 1 g with 1 g of *potassium hydrogen sulfate R* in a test tube fitted with a glass tube. Heat strongly and direct the white vapour towards a piece of filter paper impregnated with a freshly prepared 10 g/L solution of *sodium nitroprusside R*. The filter paper develops a blue colour in contact with *piperidine R*.

B. Ignite 0.1 g in a crucible. Take up the residue with 5 mL of *nitric acid R* and heat on a water-bath for 1 min. Filter. The filtrate gives reaction (b) of phosphates (*2.3.1*).

C. It gives reaction (b) of calcium (*2.3.1*).

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 1.5 g at room temperature in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 150 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*).

Acidity or alkalinity

To 100 mL of solution S add 0.1 mL of *phenolphthalein solution R*. Not more than 1.5 mL of *0.1 M hydrochloric acid* or 0.5 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Citric acid

Shake 5.0 g with 20 mL of *carbon dioxide-free water R* and filter. To the filtrate add 0.15 mL of *sulfuric acid R* and filter again. To the filtrate add 5 mL of mercuric sulfate solution R and heat to boiling. Add 0.5 mL of a 3.2 g/L solution of *potassium permanganate R* and again heat to boiling. No precipitate is formed.

Glycerol and ethanol (96 per cent)-soluble substances

Maximum 0.5 per cent.

Shake 1.000 g with 25 mL of *ethanol (96 per cent) R* for 1 min. Filter. Evaporate the filtrate on a water-bath and dry the residue at 70 °C for 1 h. The residue weighs a maximum of 5 mg.

Chlorides (*2.4.4*)

Maximum 500 ppm.

Dissolve 0.1 g in a mixture of 2 mL of *acetic acid R* and 8 mL of *water R* and dilute to 15 mL with *water R*.

Phosphates (*2.4.11*)

Maximum 400 ppm.

Dilute 2.5 mL of solution S to 100 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.1 per cent, determined on solution S.

Arsenic (*2.4.2, Method A*)

Maximum 3 ppm.

Dissolve 0.33 g in *water R* and dilute to 25 mL with the same solvent.

Iron (*2.4.9*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 50 ppm, detemined on 0.20 g.

Loss on drying (*2.2.32*)

Maximum 12.0 per cent, determined on 1.000 g by drying in an oven at 150 °C for 4 h.

ASSAY

Dissolve 0.200 g in *water R*. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 4.008 mg of Ca.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Hydrogen Phosphate[1]

General Notices

Anhydrous Calcium Hydrogen Phosphate

(Ph. Eur. monograph 0981)

$CaHPO_4$ 136.1 *7757-93-9*

Ph Eur

DEFINITION

Content

97.5 per cent to 102.5 per cent.

♦ CHARACTERS

Appearance

White or almost white, crystalline powder, or colourless crystals.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute hydrochloric acid and in dilute nitric acid.♦

IDENTIFICATION

A. Dissolve with heating 0.1 g in 10 mL of *dilute hydrochloric acid R*. Add 2.5 mL of *dilute ammonia R1*, shake, and add 5 mL of a 35 g/L solution of *ammonium oxalate R*. A white precipitate is produced.

B. Dissolve 0.1 g in 5 mL of *dilute nitric acid R*, add 2 mL of *ammonium molybdate solution R* and heat at 70 °C for 1-2 min. A yellow precipitate is produced.

◊ C. It complies with the limits of the assay.◊

TESTS

♦ Solution S

Dissolve 2.5 g in 20 mL of *dilute hydrochloric acid R*, filter if necessary and add *dilute ammonia R1* until a precipitate is formed. Add just sufficient *dilute hydrochloric acid R* to dissolve the precipitate and dilute to 50 mL with *distilled water R*.♦

Acid-insoluble substances

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.2 per cent.

Dissolve 5.0 g in 40 mL of *water R*, add 10 mL of *hydrochloric acid R* and heat to boiling for 5 min. Cool, then collect the insoluble substances using ashless filter paper. Wash with *water R* until turbidity is no longer produced when *silver nitrate solution R2* is added. Ignite the residue and the filter paper at 600 ± 50 °C. The residue weighs not more than 10 mg.

Carbonates

Shake 1.0 g with 5 mL of *carbon dioxide-free water R* and add 2 mL of *hydrochloric acid R*. No effervescence is produced.

Chlorides

Maximum 0.25 per cent.

Test solution Dissolve 0.20 g in a mixture of 20 mL of *water R* and 13 mL of *dilute nitric acid R* by warming if necessary, dilute to 100 mL with *water R* and filter if necessary. Use 50 mL of this solution.

Reference solution To 0.70 mL of *0.01 M hydrochloric acid*, add 6 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*.

Add 1 mL of *silver nitrate solution R2* to the test solution and to the reference solution and mix. After standing for 5 min protected from light, any opalescence in the test solution, by viewing vertically or horizontally against a black background, is not more intense than that in the reference solution.

♦ Fluorides

Maximum 100 ppm.

Potentiometry (*2.2.36, Method II*).

Chelating solution Dissolve 45 g of *cyclohexylenedinitrilotetra-acetic acid R* in 75 mL of *sodium hydroxide solution R* and dilute to 250 mL with *water R*.

Test solution Dissolve 1.000 g in 4 mL of *hydrochloric acid R1*, add 20 mL of chelating solution, 2.7 mL of *glacial acetic acid R* and 2.8 g of *sodium chloride R*, adjust to pH 5-6 with *sodium hydroxide solution R* and dilute to 50.0 mL with *water R*.

Reference solution Dissolve 4.42 g of *sodium fluoride R*, previously dried at 300 °C for 12 h, in *water R* and dilute to 1000.0 mL with the same solvent. Dilute 50.0 mL of this solution to 500.0 mL with *total-ionic-strength-adjustment buffer R* (200 ppm F).

Indicator electrode Fluoride-selective.

Reference electrode Silver-silver chloride.

Carry out the measurement on 20.0 mL of the test solution. Add at least 3 times 0.10 mL of the reference solution and carry out the measurement after each addition. Calculate the concentration of fluorides using the calibration curve.♦

Sulfates

Maximum 0.5 per cent.

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 0.5 g in a mixture of 5 mL of *water R* and 5 mL of *dilute hydrochloric acid R* and dilute to 100 mL with *water R*. Filter if necessary. To 20 mL of this solution, add 1 mL of *dilute hydrochloric acid R* and dilute to 50 mL with *water R*.

Reference solution To 1.0 mL of *0.005 M sulfuric acid*, add 1 mL of *dilute hydrochloric acid R* and dilute to 50 mL with *water R*. Filter if necessary.

To the test solution and to the reference solution, add 2 mL of a 120 g/L solution of *barium chloride R* and allow to stand for 10 min. Any opalescence in the test solution, by viewing vertically or horizontally against a black background, is not more intense than that in the reference solution.

♦ Arsenic (*2.4.2, Method A*)

Maximum 10 ppm, determined on 2 mL of solution S.♦

Barium

To 0.5 g, add 10 mL of *water R* and heat to boiling. While stirring, add 1 mL of *hydrochloric acid R* dropwise. Allow to cool and filter if necessary. Add 2 mL of a 10 g/L solution of *dipotassium sulfate R* and allow to stand for 10 min. No turbidity is produced.

♦ Iron (*2.4.9*)

Maximum 400 ppm.

Dilute 0.5 mL of solution S to 10 mL with *water R*.♦

Loss on ignition

6.6 per cent to 8.7 per cent, determined on 1.000 g to constant mass at 800-825 °C.

ASSAY

Dissolve 0.4 g in 12 mL of *dilute hydrochloric acid R* by heating on a water bath if necessary and dilute to 200.0 mL with *water R*. To 20.0 mL of this solution add 25.0 mL of *0.02 M sodium edetate*, 50 mL of *water R*, 5 mL of *ammonium chloride buffer solution pH 10.7 R* and about 25 mg of *mordant black 11 triturate R*. Titrate the excess of sodium edetate with *0.02 M zinc sulfate*. Carry out a blank titration.

1 mL of *0.02 M sodium edetate* is equivalent to 2.721 mg of $CaHPO_4$.

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the

www.webofpharma.com

https://thuocngocanh.com/

purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for calcium hydrogen phosphate used as filler in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*)

Bulk and tapped density (*2.9.34*)

Powder flow (*2.9.36*)◊

Ph Eur

1 This monograph has undergone the process of Pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Hydrogen Phosphate Dihydrate[1]

General Notices

Dibasic Calcium Phosphate

(Ph. Eur. monograph 0116)

NOTE: *The name Calcium Hydrogen Phosphate was formerly used in the United Kingdom.*

$CaHPO_4,2H_2O$ 172.1 *7789-77-7*

Ph Eur

DEFINITION

Content

98.0 per cent to 105.0 per cent.

♦ CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute hydrochloric acid and in dilute nitric acid.♦

IDENTIFICATION

A. Dissolve with heating 0.1 g in 10 mL of *dilute hydrochloric acid R*. Add 2.5 mL of *dilute ammonia R1*, shake and add 5 mL of a 35 g/L solution of *ammonium oxalate R*. A white precipitate is produced.

B. Dissolve 0.1 g in 5 mL of *dilute nitric acid R*, add 2 mL of *ammonium molybdate solution R* and heat at 70 °C for 2 min. A yellow precipitate is produced.

◊ C. It complies with the limits of the assay.◊

TESTS

Solution S

Dissolve 2.5 g in 20 mL of *dilute hydrochloric acid R*, filter if necessary and add *dilute ammonia R1* until a precipitate is formed. Add just sufficient *dilute hydrochloric acid R* to dissolve the precipitate and dilute to 50 mL with *distilled water R*.

www.webofpharma.com

https://thuocngocanh.com/

Acid-insoluble substances

Maximum 0.2 per cent.

Dissolve 5.0 g in 40 mL of *water R*, add 10 mL of *hydrochloric acid R* and heat to boiling for 5 min. Cool, then collect the insoluble substances using ashless filter paper. Wash with *water R* until turbidity is no longer produced when *silver nitrate solution R2* is added to the filtrate. Ignite at 600 ± 50 °C. The residue weighs not more than 10 mg.

Carbonates

Shake 0.5 g with 5 mL of *carbon dioxide-free water R* and add 1 mL of *hydrochloric acid R*. No effervescence is produced.

Chlorides

Maximum 0.25 per cent.

Test solution Dissolve 0.20 g in a mixture of 20 mL of *water R* and 13 mL of *dilute nitric acid R* by warming if necessary, dilute to 100 mL with *water R* and filter if necessary. Use 50 mL of this solution.

Reference solution To 0.70 mL of *0.01 M hydrochloric acid*, add 6 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*.

Add 1 mL of *silver nitrate solution R2* to the test solution and to the reference solution and mix. After standing for 5 min protected from light, any opalescence in the test solution is not more intense than that in the reference solution.

♦ Fluorides

Maximum 100 ppm.

Potentiometry (*2.2.36, Method II*).

Chelating solution Dissolve 45 g of *cyclohexylenedinitrilotetra-acetic acid R* in 75 mL of *sodium hydroxide solution R* and dilute to 250 mL with *water R*.

Test solution Dissolve 1.000 g in 4 mL of *hydrochloric acid R1*, add 20 mL of chelating solution, 2.7 mL of *glacial acetic acid R* and 2.8 g of *sodium chloride R*, adjust to pH 5-6 with *sodium hydroxide solution R* and dilute to 50.0 mL with *water R*.

Reference solution Dissolve 4.42 g of *sodium fluoride R*, previously dried at 300 °C for 12 h, in *water R* and dilute to 1000.0 mL with the same solvent. Dilute 50.0 mL of this solution to 500.0 mL with *total-ionic-strength-adjustment buffer R* (200 ppm F).

Indicator electrode Fluoride-selective.

Reference electrode Silver-silver chloride.

Carry out the measurement on 20.0 mL of the test solution. Add at least 3 times 0.10 mL of the reference solution and carry out the measurement after each addition. Calculate the concentration of fluorides using the calibration curve.♦

Sulfates

Maximum 0.5 per cent.

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 0.5 g in a mixture of 5 mL of *water R* and 5 mL of *dilute hydrochloric acid R* and dilute to 100 mL with *water R*. Filter if necessary. To 20 mL of this solution, add 1 mL of *dilute hydrochloric acid R* and dilute to 50 mL with *water R*.

Reference solution To 1.0 mL of *0.005 M sulfuric acid*, add 1 mL of *dilute hydrochloric acid R* and dilute to 50 mL with *water R*. Filter if necessary.

To the test solution and to the reference solution, add 2 mL of a 120 g/L solution of *barium chloride R* and allow to stand for 10 min. Any opalescence in the test solution is not more intense than that in the reference solution.

♦ Arsenic (*2.4.2, Method A*)

Maximum 10 ppm, determined on 2 mL of solution S.♦

Barium

To 0.5 g, add 10 mL of *water R* and heat to boiling. While stirring, add 1 mL of *hydrochloric acid R* dropwise. Allow to cool and filter if necessary. Add 2 mL of a 10 g/L solution of *dipotassium sulfate R* and allow to stand for 10 min. No turbidity is produced.

♦ Iron (*2.4.9*)

Maximum 400 ppm.

Dilute 0.5 mL of solution S to 10 mL with *water R*.♦

Loss on ignition

24.5 per cent to 26.5 per cent, determined on 1.000 g by ignition to constant mass at 800-825 °C.

ASSAY

Dissolve 0.4 g in 12 mL of *dilute hydrochloric acid R* by heating on a water bath if necessary and dilute to 200 mL with *water R*. To 20.0 mL of this solution add 25.0 mL of *0.02 M sodium edetate*, 50 mL of *water R*, 5 mL of *ammonium chloride buffer solution pH 10.7 R* and about 25 mg of *mordant black 11 triturate R*. Titrate the excess of sodium edetate with *0.02 M zinc sulfate*. Carry out a blank titration.

1 mL of *0.02 M sodium edetate* is equivalent to 3.44 mg of $CaHPO_4,2H_2O$.

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

www.webofpharma.com

https://thuathuocngocanh.com/

The following characteristics may be relevant for calcium hydrogen phosphate dihydrate used as filler in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*)

Bulk and tapped density (*2.9.34*)

Powder flow (*2.9.36*)◊

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8. Pharmacopoeial harmonisation*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Hydroxide

General Notices

(Ph. Eur. monograph 1078)

$Ca(OH)_2$ 74.1 *1305-62-0*

Preparation

Calcium Hydroxide Solution

Ph Eur

DEFINITION

Content

95.0 per cent to 100.5 per cent.

CHARACTERS

Appearance

White or almost white, fine powder.

Solubility

Practically insoluble in water.

IDENTIFICATION

A. To 0.80 g in a mortar, add 10 mL of *water R* and 0.5 mL of *phenolphthalein solution R* and mix. The suspension turns red. On addition of 17.5 mL of a 103 g/L solution of *hydrochloric acid R*, the suspension becomes colourless without effervescing. The red colour occurs again when the mixture is triturated for 1 min. On addition of a further 6 mL of a 103 g/L solution of *hydrochloric acid R* and triturating, the solution becomes colourless.

B. Dissolve about 0.1 g in *dilute hydrochloric acid R* and dilute to 10 mL with *water R*. 5 mL of the solution give reaction (b) of calcium (*2.3.1*).

TESTS

Matter insoluble in hydrochloric acid

Maximum 0.5 per cent.

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 2.0 g in 30 mL of *hydrochloric acid R*. Boil the solution and filter. Wash the residue with hot *water R*. The residue weighs a maximum of 10 mg.

Carbonates

Maximum 5.0 per cent of $CaCO_3$.

Add 5.0 mL of *1 M hydrochloric acid* to the titrated solution obtained under Assay and titrate with *1 M sodium hydroxide* using 0.5 mL of *methyl orange solution R* as indicator.

1 mL of *1 M hydrochloric acid* is equivalent to 50.05 mg of $CaCO_3$.

Chlorides (*2.4.4*)

Maximum 330 ppm.

Dissolve 0.30 g in a mixture of 2 mL of *nitric acid R* and 10 mL of *water R* and dilute to 30 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.4 per cent.

Dissolve 0.15 g in a mixture of 5 mL of *dilute hydrochloric acid R* and 10 mL of *distilled water R* and dilute to 60 mL with *distilled water R*.

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20*. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Cadmium	1
Lead	1

Magnesium and alkali metals

Maximum 4.0 per cent, calculated as sulfates.

Dissolve 1.0 g in a mixture of 10 mL of *hydrochloric acid R* and 40 mL of *water R*. Boil and add 50 mL of a 63 g/L solution of *oxalic acid R*. Neutralise with *ammonia R* and dilute to 200 mL with *water R*. Allow to stand for 1 h and filter through a suitable filter. To 100 mL of the filtrate, add 0.5 mL of *sulfuric acid R*. Cautiously evaporate to dryness and ignite. The residue weighs a maximum of 20 mg.

ASSAY

To 1.500 g in a mortar, add 20-30 mL of *water R* and 0.5 mL of *phenolphthalein solution R*. Titrate with *1 M hydrochloric acid* by triturating the substance until the red colour disappears. The final solution is used in the tests for carbonates.

1 mL of *1 M hydrochloric acid* is equivalent to 37.05 mg of $Ca(OH)_2$.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Hydroxide Solution

General Notices

Lime Water

DEFINITION

Calcium Hydroxide	10 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

Extemporaneous preparation

The following directions apply.

Shake together thoroughly and repeatedly; allow to stand until clear. Siphon off the clear solution as required.

Content of calcium hydroxide, $Ca(OH)_2$

Not less than 0.15% w/v.

CHARACTERISTICS

A colourless liquid. It absorbs carbon dioxide from the air, a film of calcium carbonate being formed on the surface of the liquid. It becomes turbid when boiled and clear again on cooling.

IDENTIFICATION

Yields the reactions characteristic of *calcium salts*, Appendix VI.

ASSAY

Titrate 25 mL with *0.1M hydrochloric acid VS* using *phenolphthalein solution R1* as indicator. Each mL of *0.1M hydrochloric acid VS* is equivalent to 3.705 mg of $Ca(OH)_2$.

STORAGE

Calcium Hydroxide Solution should be kept in a well-filled container.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

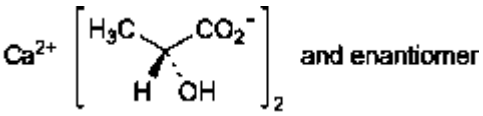
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Lactate

General Notices

Anhydrous Calcium Lactate

(Ph. Eur. monograph 2118)



$C_6H_{10}CaO_6$ 218.2

Action and use

Used in treatment of calcium deficiency.

Ph Eur

DEFINITION

Calcium bis(2-hydroxypropanoate) or mixture of calcium (2*R*)-, (2*S*)- and (2*RS*)-2-hydroxypropanoates.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or granular powder.

Solubility

Soluble in water, freely soluble in boiling water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Loss on drying (see Tests).

B. It gives the reaction of lactates (*2.3.1*).

C. It gives reaction (b) of calcium (*2.3.1*).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 5.0 g with heating in *carbon dioxide-free water R* prepared from *distilled water R*, allow to cool and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R* and 0.5 mL of *0.01 M hydrochloric acid*. The solution is colourless. Not more than 2.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 400 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Barium

To 10 mL of solution S add 1 mL of *calcium sulfate solution R*. Allow to stand for 15 min. Any opalescence in the solution is not more intense than that in a mixture of 1 mL of *distilled water R* and 10 mL of solution S.

Iron (*2.4.9*)

Maximum 50 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Magnesium and alkali salts

Maximum 1 per cent.

To 20 mL of solution S add 20 mL of *water R*, 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*. Heat to boiling and rapidly add 40 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 100.0 mL with *water R* and filter. To 50.0 mL of the filtrate add 0.5 mL of *sulfuric acid R*. Evaporate to dryness and ignite the residue to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

Loss on drying (*2.2.32*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 3.0 per cent, determined on 0.500 g by drying in an oven at 125 °C.

ASSAY

Dissolve 0.200 g in *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 21.82 mg of $C_6H_{10}CaO_6$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

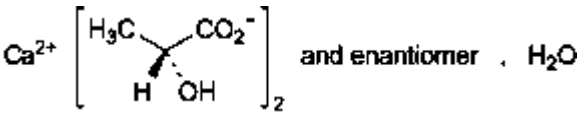
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Lactate Monohydrate

General Notices

(Ph. Eur. monograph 2117)



$C_6H_{10}CaO_6,H_2O$ 236.2

Action and use

Used in treatment of calcium deficiency.

Ph Eur

DEFINITION

Calcium bis[(2Ξ)-2-hydroxypropanoate] or mixture of calcium (2*R*)-, (2*S*)- and (2*RS*)-2-hydroxypropanoates monohydrates.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or granular powder.

Solubility

Soluble in water, freely soluble in boiling water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Loss on drying (see Tests).

B. It gives the reaction of lactates (*2.3.1*).

C. It gives reaction (b) of calcium (*2.3.1*).

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 5.4 g (equivalent to 5.0 g of the dried substance) with heating in *carbon dioxide-free water R* prepared from *distilled water R*, allow to cool and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R* and 0.5 mL of *0.01 M hydrochloric acid*. The solution is colourless. Not more than 2.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 400 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 50 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Magnesium and alkali salts

Maximum 1 per cent.

To 20 mL of solution S add 20 mL of *water R*, 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*. Heat to boiling and rapidly add 40 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 100.0 mL with *water R* and filter. To 50.0 mL of the filtrate add 0.5 mL of *sulfuric acid R*. Evaporate to dryness and ignite the residue to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

Loss on drying (*2.2.32*)

5.0 per cent to 8.0 per cent, determined on 0.500 g by drying in an oven at 125 °C.

ASSAY

Dissolve a quantity equivalent to 0.200 g of the dried substance in *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of calcium (*2.5.11*).

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *0.1 M sodium edetate* is equivalent to 21.82 mg of $C_6H_{10}CaO_6$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

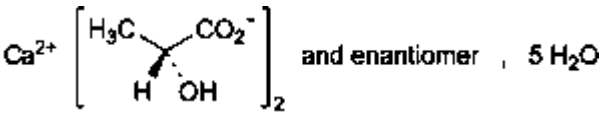
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Lactate Pentahydrate

General Notices

Calcium Lactate

(Ph. Eur. monograph 0468)



$C_6H_{10}CaO_6,5H_2O$ 308.3

Action and use

Used in treatment of calcium deficiency.

Preparations

Calcium and Ergocalciferol Tablets

Calcium Lactate Tablets

Calcium and Ergocalciferol Chewable Tablets

Ph Eur

DEFINITION

Calcium bis[(2Ξ)-2-hydroxypropanoate] or mixture of calcium (2*R*)-, (2*S*)- and (2*RS*)-2-hydroxypropanoates pentahydrates.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or granular powder, slightly efflorescent.

Solubility

Soluble in water, freely soluble in boiling water, very slightly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Loss on drying (see Tests).

B. It gives the reaction of lactates (2.3.1).

C. It gives reaction (b) of calcium (2.3.1).

TESTS

Solution S

Dissolve 7.1 g (equivalent to 5.0 g of the dried substance) with heating in *carbon dioxide-free water R* prepared from *distilled water R*, allow to cool and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R* and 0.5 mL of *0.01 M hydrochloric acid*. The solution is colourless. Not more than 2.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Chlorides (2.4.4)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 400 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Iron (2.4.9)

Maximum 50 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Magnesium and alkali salts

Maximum 1 per cent.

To 20 mL of solution S add 20 mL of *water R*, 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*. Heat to boiling and rapidly add 40 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 100.0 mL with *water R* and filter. To 50.0 mL of the filtrate add

www.webofpharma.com

https://thuathuocngocanh.com/

0.5 mL of *sulfuric acid R*. Evaporate to dryness and ignite the residue to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

Loss on drying (*2.2.32*)

22.0 per cent to 27.0 per cent, determined on 0.500 g by drying in an oven at 125 °C.

ASSAY

Dissolve a quantity equivalent to 0.200 g of the dried substance in *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 21.82 mg of $C_6H_{10}CaO_6$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Lactate Tablets

General Notices

DEFINITION

Calcium Lactate Tablets contain Calcium Lactate Pentahydrate or Calcium Lactate Trihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of calcium lactate, calculated as $C_6H_{10}CaO_6,5H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Triturate a quantity of the powdered tablets containing 0.3 g of Calcium Lactate Pentahydrate or its equivalent with 5 mL of *methanol* and filter. To 0.2 mL of the filtrate add 2 mL of *sulfuric acid*, heat at 85° for 2 minutes, cool and add 4 mg of *4-hydroxybiphenyl*. A violet-red colour is produced.

B. The powdered tablets, when moistened with *hydrochloric acid* and introduced on a platinum wire into a flame, impart a brick red colour to the flame.

Disintegration

Maximum time, 30 minutes, Appendix XII A1.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.3 g of Calcium Lactate Pentahydrate or its equivalent as completely as possible in 50 mL of *water* and titrate with 0.05M *disodium edetate VS* to within a few millilitres of the expected end point. Add 8 mL of 5M *sodium hydroxide* and 0.1 g of *solochrome dark blue mixture* and continue the titration until the colour changes from pink to full blue. Each mL of 0.05M *disodium edetate VS* is equivalent to 15.41 mg of $C_6H_{10}CaO_6,5H_2O$.

LABELLING

When the active ingredient is Calcium Lactate Trihydrate the quantity is stated in terms of the equivalent amount of Calcium Lactate Pentahydrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

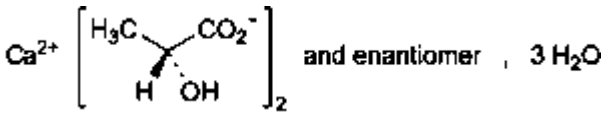
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Lactate Trihydrate

General Notices

(Ph. Eur. monograph 0469)



$C_6H_{10}CaO_6,3H_2O$ 272.3

Action and use

Used in treatment of calcium deficiency.

Preparation

Calcium Lactate Tablets

Ph Eur

DEFINITION

Calcium bis[(2Ξ)-2-hydroxypropanoate] or mixture of calcium (2*R*)-, (2*S*)- and (2*RS*)-2-hydroxypropanoates trihydrates.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or granular powder.

Solubility

Soluble in water, freely soluble in boiling water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Loss on drying (see Tests).

B. It gives the reaction of lactates (2.3.1).

C. It gives reaction (b) of calcium (2.3.1).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 6.2 g (equivalent to 5.0 g of the dried substance) with heating in *carbon dioxide-free water R* prepared from *distilled water R*, allow to cool and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R* and 0.5 mL of *0.01 M hydrochloric acid*. The solution is colourless. Not more than 2.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 400 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 50 ppm.

Dilute 4 mL of solution S to 10 mL with *water R*.

Magnesium and alkali salts

Maximum 1 per cent.

To 20 mL of solution S add 20 mL of *water R*, 2 g of *ammonium chloride R* and 2 mL of *dilute ammonia R1*. Heat to boiling and rapidly add 40 mL of hot *ammonium oxalate solution R*. Allow to stand for 4 h, dilute to 100.0 mL with *water R* and filter. To 50.0 mL of the filtrate add 0.5 mL of *sulfuric acid R*. Evaporate to dryness and ignite the residue to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5 mg.

Loss on drying (*2.2.32*)

15.0 per cent to 20.0 per cent, determined on 0.500 g by drying in an oven at 125 °C.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Dissolve a quantity equivalent to 0.200 g of the dried substance in *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of calcium (2.5.11).

1 mL of *0.1 M sodium edetate* is equivalent to 21.82 mg of $C_6H_{10}CaO_6$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

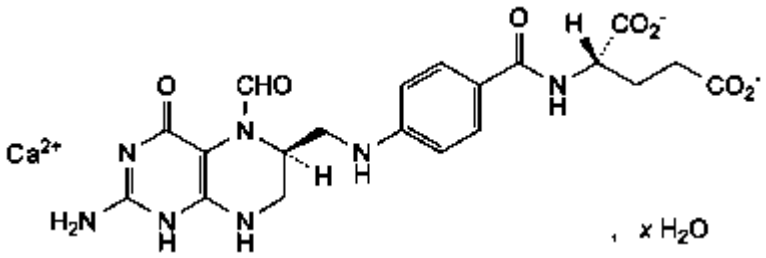
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Levofolinate Hydrate

General Notices

Calcium Levofolinate Pentahydrate

(Ph. Eur. monograph 1606)



$C_{20}H_{21}CaN_7O_7,xH_2O$ 511.5 (anhydrous substance)

Action and use

Antidote to folic acid antagonists.

Ph Eur

DEFINITION

Calcium (2*S*)-2-[4-[[[(6*S*)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzamido]pentanedioate hydrate.

Content

— *calcium levofolinate* ($C_{20}H_{21}CaN_7O_7$; M_r 511.5): 97.0 per cent to 102.0 per cent (anhydrous substance);

— *calcium* (Ca; A_r 40.08): 7.54 per cent to 8.14 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or light yellow, amorphous or crystalline, hygroscopic powder.

Solubility

Slightly soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

www.webofpharma.com

https://thuvienthuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B, D.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison: calcium folinate CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum quantity of water R and add dropwise sufficient acetone R to produce a precipitate. Allow to stand for 15 min, collect the precipitate by centrifugation, wash the precipitate twice with a minimum quantity of acetone R and dry. Record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 15 mg of the substance to be examined in a 3 per cent *V/V* solution of ammonia R and dilute to 5 mL with the same solvent.

Reference solution Dissolve 15 mg of calcium folinate CRS in a 3 per cent *V/V* solution of ammonia R and dilute to 5 mL with the same solvent.

Plate cellulose for chromatography F_{254} R as the coating substance.

Mobile phase The lower layer of a mixture of 1 volume of isoamyl alcohol R and 10 volumes of a 50 g/L solution of citric acid monohydrate R previously adjusted to pH 8 with ammonia R.

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (b) of calcium (2.3.1).

TESTS

Carry out the tests and the assay as rapidly as possible, protected from actinic light.

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.40 g in *carbon dioxide-free water R*, heating at 40 °C if necessary, and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*).

pH (*2.2.3*)

7.5 to 8.5 for solution S.

Specific optical rotation (*2.2.7*)

-15.0 to -10.0 (anhydrous substance), measured at 25 °C.

Dissolve 0.200 g in *tris(hydroxymethyl)aminomethane solution R* previously adjusted to pH 8.1 with *sodium hydroxide solution R* or *hydrochloric acid R1* and dilute to 20.0 mL with the same solvent.

Absorbance (*2.2.25*)

Maximum 0.25, determined at 420 nm on solution S.

Ethanol

Head-space gas chromatography (*2.2.28*): use the standard additions method.

Test solution Dissolve 0.25 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dilute 0.750 g of *anhydrous ethanol R* to 1000.0 mL with *water R*.

Column:

— *material*: fused silica;

— *size*: *l* = 10 m, Ø = 0.32 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 4 mL/min.

Static head-space conditions that may be used:

— *equilibration temperature*: 80 °C;

— *equilibration time*: 20 min;

— *pressurisation time*: 30 s.

Temperature:

www.webofpharma.com

https://nhathuocngocanh.com/

	Time (min)	Temperature (°C)
Column	0 - 14	80 → 220
Injection port		110
Detector		270

Detection Flame ionisation.

Injection At least 3 times.

Limit:

— *ethanol*: maximum 3.0 per cent.

Related substances

Liquid chromatography (2.2.29).

Prepare the solutions immediately before use.

Test solution Dissolve 10.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *calcium folinate CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (c) Dissolve 5 mg of *calcium folinate for system suitability CRS* (containing impurities A, E, F and I) in 5 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 165 mL of *methanol R* and 835 mL of a solution containing 4.0 mL of *tetrabutylammonium dihydrogen phosphate solution R* and 1.42 g of *disodium hydrogen phosphate dihydrate R* in *water for chromatography R*, previously adjusted to pH 7.7 with *phosphoric acid R* or *dilute sodium hydroxide solution R*.

Flow rate 1.25 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time 4 times the retention time of folinic acid.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *calcium folinate for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, E, F and I.

Relative retention With reference to folinic acid (retention time = about 13.9 min): impurity E = about 0.4; impurity A = about 0.6; impurity F = about 0.7; impurity I = about 1.2.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to impurities A and F.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity E = 0.6; impurity F = 0.6; impurity I = 0.6;

— for each impurity, use the concentration of calcium levofolinate hydrate in reference solution (b).

Limits:

— *impurities A, E*: for each impurity, maximum 0.3 per cent;

— *impurities F, I*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.20 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Impurity H

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *calcium folinate CRS* in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4 mm;

— *stationary phase*: human albumin coated silica gel for chiral separation R (5 µm);

— *temperature*: 40 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Dissolve 9.72 g of *sodium dihydrogen phosphate R* in 890 mL of *water for chromatography R* and adjust to pH 5.0 with *sodium hydroxide solution R*; add 100 mL of *2-propanol R* and 10 mL of *acetonitrile R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 286 nm.

Injection 10 µL.

Retention times Levofolinic acid = about 9 min; impurity H = about 19 min.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to levofolinic acid and impurity H in the chromatogram obtained with reference solution (a). The sum of the areas of the 2 peaks is 100 per cent. The peak area of impurity H is 48 per cent to 52 per cent. In the chromatogram obtained with reference solution (b) 2 clearly visible peaks are obtained.

Limit:

— *impurity H*: maximum 0.5 per cent.

Chlorides

Maximum 0.5 per cent.

Dissolve 0.300 g in 50 mL of *water R* heating at 40 °C if necessary. Add 10 mL of *dilute nitric acid R* and titrate with *0.005 M silver nitrate* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.005 M silver nitrate* is equivalent to 0.177 mg of Cl.

Water

(*2.5.12*): 10.0 per cent to 17.0 per cent.

Dissolve 0.100 g in a mixture of 15 mL of *formamide R* and 50 mL of the titration solvent. Stir for about 6 min before titrating and use a suitable titrant that does not contain pyridine.

ASSAY

Carry out the assays as rapidly as possible, protected from actinic light.

Calcium

Dissolve 0.400 g in 150 mL of *water R* and dilute to 300 mL with the same solvent. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 4.008 mg of Ca.

Calcium folinate

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{20}H_{21}CaN_7O_7$ taking into account the assigned content of *calcium folinate CRS*.

STORAGE

In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

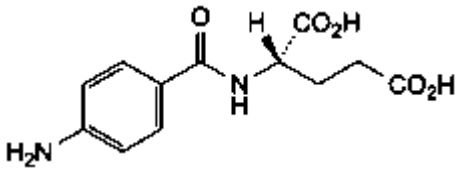
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

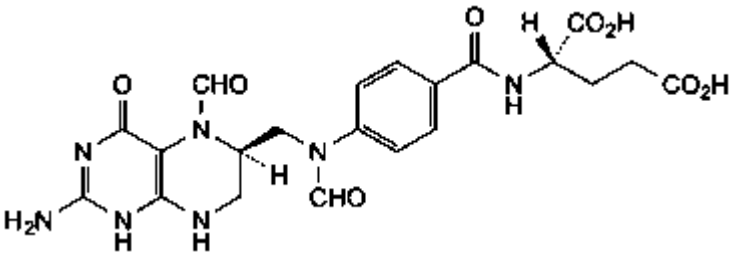
IMPURITIES

Specified impurities *A, E, F, H, I.*

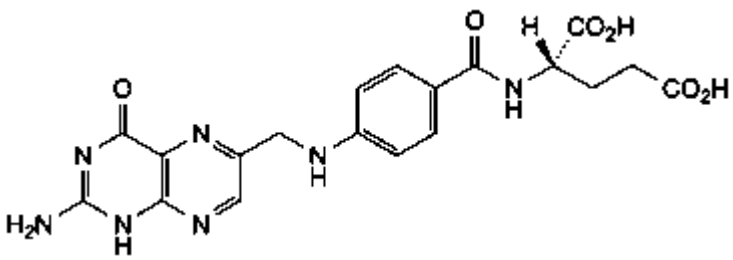
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, G.*



A. (2*S*)-2-(4-aminobenzamido)pentanedioic acid,



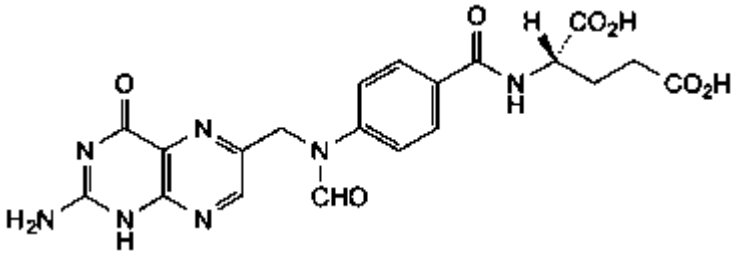
B. (2*S*)-2-[4-[[[(6*R*)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl](formyl)amino]benzamido]pentanedioic acid (5,10-diformyltetrahydrolevofolic acid),



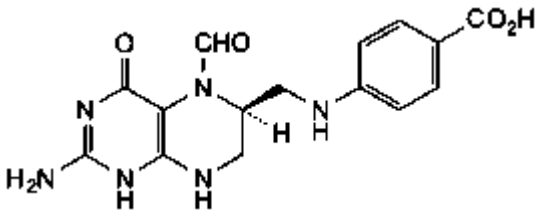
www.webofpharma.com

https://thuocngocanh.com/

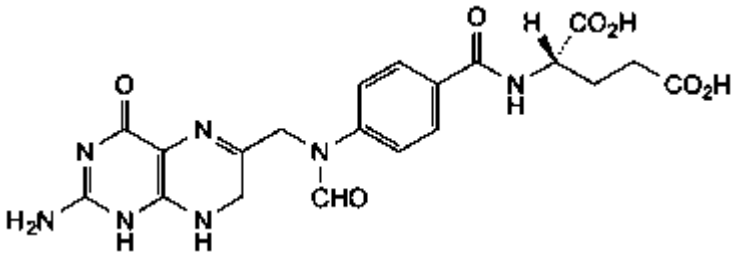
C. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino]benzamido]pentanedioic acid (folic acid),



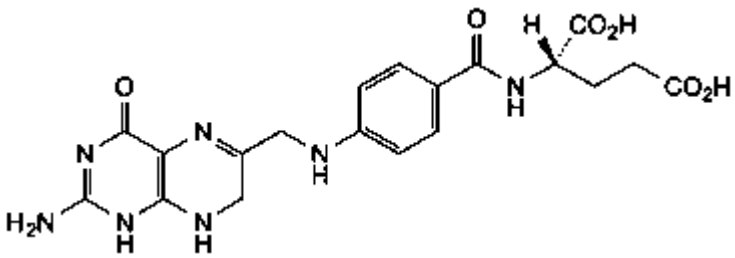
D. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl](formyl)amino]benzamido]pentanedioic acid (10-formylfolic acid),



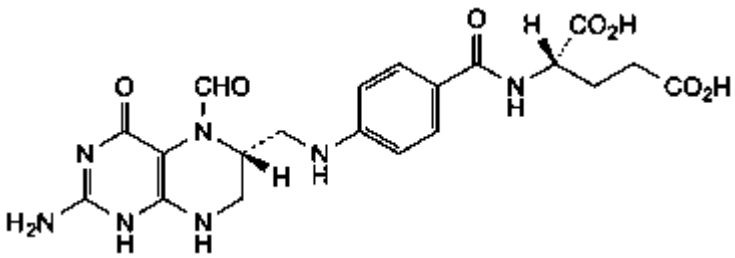
E. 4-[[[(6*S*)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzoic acid ((6*S*)-5-formyltetrahydropteroic acid),



F. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4,7,8-tetrahydropteridin-6-yl)methyl](formyl)amino]benzamido]pentanedioic acid (10-formyldihydrofolic acid),



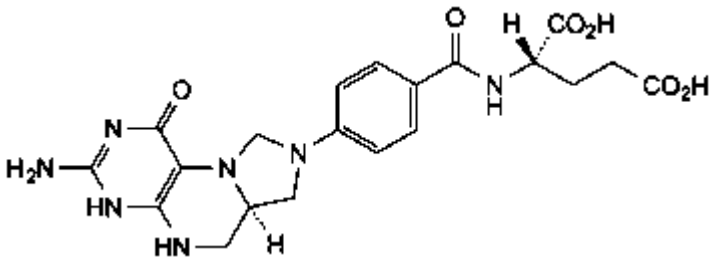
G. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4,7,8-tetrahydropteridin-6-yl)methyl]amino]benzamido]pentanedioic acid (dihydrofolic acid),



www.webofpharma.com

https://thuvienthuocngocanh.com/

H. (2*S*)-2-[4-[[[(6*R*)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzamido]pentanedioic acid (dextrofolinic acid),



I. (2*S*)-2-[4-[(6a*R*)-3-amino-1-oxo-1,2,5,6,6a,7-hexahydroimidazo[1,5-*f*]pteridin-8(9*H*)-yl]benzamido]pentanedioic acid ((6a*R*)-5,10-methylenetetrahydrofolic acid).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

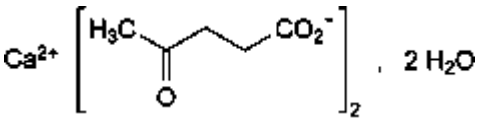
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Levulinate Dihydrate

General Notices

(Ph. Eur. monograph 1296)



$C_{10}H_{14}CaO_6,2H_2O$ 306.3 *5743-49-7*

Action and use

Source of calcium.

Ph Eur

DEFINITION

Calcium di(4-oxopentanoate) dihydrate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, D, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *calcium levulinate dihydrate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 60 mg of the substance to be examined in water R and dilute to 1 mL with the same solvent.

Reference solution Dissolve 60 mg of calcium levulinate dihydrate CRS in water R and dilute to 1 mL with the same solvent.

Plate TLC silica gel plate R.

Mobile phase concentrated ammonia R, ethyl acetate R, water R, ethanol (96 per cent) R (10:10:30:50 *V/V/V/V*).

Application 10 µL.

Development Over a path of 10 cm.

Drying At 100-105 °C for 20 min and allow to cool.

Detection Spray with a 30 g/L solution of potassium permanganate R. Dry in a current of warm air for about 5 min or until the spots become yellow. Examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 1 mL of solution S (see Tests), add 20 mL of a 2.5 g/L solution of dinitrophenylhydrazine R in dilute hydrochloric acid R. Allow to stand for 15 min. Filter, wash the precipitate with water R. Dry the precipitate in an oven at 100-105 °C. The melting point (2.2.14) is 203 °C to 210 °C.

D. It gives reaction (b) of calcium (2.3.1).

E. Loss on drying (see Tests).

TESTS

Solution S

Dissolve 10.0 g in carbon dioxide-free water R prepared from distilled water R and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

pH (2.2.3)

6.8 to 7.8 for solution S.

Oxidisable substances

To 1 mL of solution S, add 10 mL of water R, 1 mL of dilute sulfuric acid R and 0.25 mL of a 3.0 g/L solution of potassium permanganate R. Mix. After 5 min, the violet colour of the mixture is still visible.

Sucrose and reducing sugars

www.webofpharma.com

https://thuvienthuocngocanh.com/

To 5 mL of solution S add 2 mL of *hydrochloric acid R1* and dilute to 10 mL with *water R*. Heat to boiling for 5 min and allow to cool. Add 10 mL of *sodium carbonate solution R*. Allow to stand for 5 min, dilute to 25 mL with *water R* and filter. To 5 mL of the filtrate add 2 mL of *cupri-tartaric solution R* and heat to boiling for 1 min. No red precipitate is formed.

Chlorides (*2.4.4*)

Maximum 50 ppm.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 200 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Magnesium and alkali metals

Maximum 1.0 per cent.

To 10 mL of solution S, add 80 mL of *water R*, 10 mL of *ammonium chloride solution R* and 1 mL of *ammonia R*. Heat to boiling. To the boiling solution, add dropwise 50 mL of warm *ammonium oxalate solution R*. Allow to stand for 4 h, then dilute to 200 mL with *water R* and filter. To 100 mL of the filtrate, add 0.5 mL of *sulfuric acid R*. Evaporate to dryness on a water-bath and ignite to constant mass at 600 ± 50 °C. The residue weighs a maximum of 5.0 mg.

Loss on drying (*2.2.32*)

11.0 per cent to 12.5 per cent, determined on 0.200 g by drying at 105 °C.

Pyrogens (*2.6.8*)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of pyrogens, it complies with the test for pyrogens. Inject per kilogram of the rabbit's mass 4 mL of a solution containing per millilitre 50 mg of the substance to be examined.

ASSAY

Dissolve 0.240 g in 50 mL of *water R*. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 27.03 mg of $C_{10}H_{14}CaO_6$.

STORAGE

Protected from light.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuvienthuocngocanh.com/

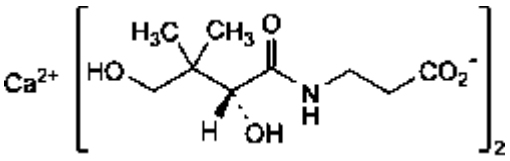
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Calcium Pantothenate

General Notices

(Ph. Eur. monograph 0470)



$C_{18}H_{32}CaN_2O_{10}$ 476.5 *137-08-6*

Action and use

Component of vitamin B.

Ph Eur

DEFINITION

Calcium bis[3-[(2*R*)-2,4-dihydroxy-3,3-dimethylbutanamido]propanoate].

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent) and practically insoluble in heptane.

IDENTIFICATION

First identification: A, B, D.

Second identification: C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *calcium pantothenate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of 0.25 mL of *water R* and 4 mL of *methanol R*.

Reference solution Dissolve 10 mg of *calcium pantothenate CRS* in a mixture of 0.25 mL of *water R* and 4 mL of *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *2-propanol R* (5:15:80 *V/V/V*).

Application 5 µL.

Development Over 4/5 of the plate.

Drying In air.

Detection Heat at 120 °C for 20 min; treat the warm plate with a 3 g/L solution of *ninhydrin R* in a mixture of 3 volumes of *glacial acetic acid R* and 100 volumes of *anhydrous ethanol R*; allow to dry and heat again at 120 °C for a few minutes; examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of calcium (2.3.1); use *methylene chloride R* instead of *chloroform R* for the extraction.

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

6.8 to 8.0 for solution S.

Specific optical rotation (2.2.7)

+ 25.5 to + 27.5 (dried substance), determined on solution S.

Impurity A and other aminocarboxylic acid impurities

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.50 per cent.

Dissolve 8.000 g in 40 mL of *water R* and dilute to 100 mL with the same solvent. Add 25 mL of *formaldehyde solution R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 8.91 mg of $C_3H_7NO_2$.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.600 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 30.0 mg of *calcium pantothenate CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (c) Dissolve 3.0 mg of *pantolactone CRS* (impurity C) in 5.0 mL of *water R*. Mix 1.0 mL of the solution and 1.0 mL of reference solution (a) and dilute to 100.0 mL with the same solvent.

Reference solution (d) Dissolve 3 mg of *pantothenate for peak identification CRS* (containing impurities B, E and H) in 0.5 mL of *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 1 volume of *acetonitrile R1* and 99 volumes of a 1.56 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 2.5 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	100	0
6 - 21	100 → 50	0 → 50
21 - 30	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 5 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C; use the chromatogram supplied with *pantothenate for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B, E and H.

Relative retention With reference to calcium pantothenate (retention time = about 4 min): impurity B = about 0.5; impurity C = about 0.8; impurity E = about 1.7; impurity H = about 2.3.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to impurity C and calcium pantothenate;

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity C.

Calculation of percentage contents:

— for impurities B and C, use the concentration of impurity C in reference solution (c);

— for impurities other than B and C, use the concentration of calcium pantothenate in reference solution (b).

Limits:

— *impurity B*: maximum 0.8 per cent;

— *impurity C*: maximum 0.3 per cent;

— *impurity E*: maximum 0.25 per cent;

— *impurity H*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.2 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak due to impurity A (eluting before 1 min).

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.180 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 23.83 mg of $C_{18}H_{32}CaN_2O_{10}$.

STORAGE

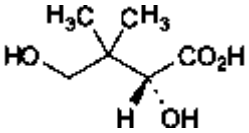
In an airtight container.

IMPURITIES

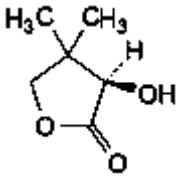
Specified impurities *A, B, C, E, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, F, G.*

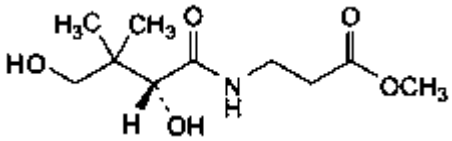
A. 3-aminopropanoic acid (β-alanine),



B. (2*R*)-2,4-dihydroxy-3,3-dimethylbutanoic acid (pantoic acid),



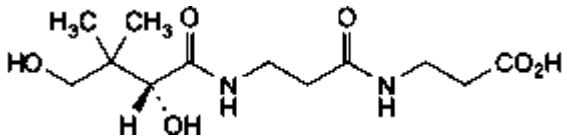
C. (3*R*)-3-hydroxy-4,4-dimethyloxolan-2-one (pantolactone),



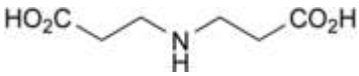
D. methyl 3-[(2*R*)-2,4-dihydroxy-3,3-dimethylbutanamido]propanoate (methyl pantothenate),

www.webofpharma.com

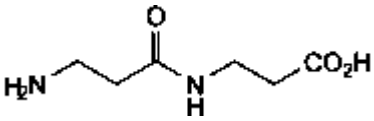
https://thuocngocanh.com/



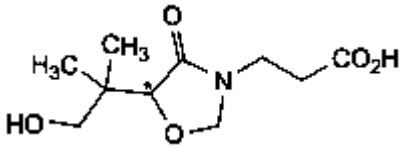
E. 3-[3-[(2*R*)-2,4-dihydroxy-3,3-dimethylbutanamido]propanamido]propanoic acid (β-alanyl pantothenamide),



F. 3,3′-azanediyldipropanoic acid,



G. 3-(3-aminopropanamido)propanoic acid (β-alanyl-β-alanine),



H. 3-[(5Ξ)-5-(1-hydroxy-2-methylpropan-2-yl)-4-oxo-1,3-oxazolidin-3-yl]propanoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Phosphate

General Notices

Tribasic Calcium Phosphate

(Ph. Eur. monograph 1052)

Action and use

Excipient.

Preparations

Calcium and Ergocalciferol Tablets

Calcium Phosphate for Homoeopathic Preparations

Calcium and Ergocalciferol Chewable Tablets

Ph Eur

DEFINITION

Mixture of calcium phosphates.

Content

35.0 per cent to 40.0 per cent of Ca (A_r 40.08).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water. It dissolves in dilute hydrochloric acid and in dilute nitric acid.

IDENTIFICATION

A. Dissolve 0.1 g in 5 mL of a 25 per cent *V/V* solution of *nitric acid R*. The solution gives reaction (b) of phosphates (2.3.1).

B. It gives reaction (b) of calcium (2.3.1). Filter before adding *potassium ferrocyanide solution R*.

C. It complies with the limits of the assay.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 1.00 g in 8 mL of *dilute hydrochloric acid R*. If the solution is not clear, filter it. Add *dilute ammonia R1* dropwise until a precipitate is formed. Dissolve the precipitate by adding *dilute hydrochloric acid R* and dilute to 20 mL with *distilled water R*.

Chlorides (*2.4.4*)

Maximum 0.15 per cent.

Dissolve 0.22 g in a mixture of 1 mL of *nitric acid R* and 10 mL of *water R* and dilute to 100 mL with *water R*.

Fluorides

Maximum 75 ppm.

Potentiometry (*2.2.36, Method II*).

Test solution Dissolve 0.250 g in *0.1 M hydrochloric acid*, add 5.0 mL of *fluoride standard solution (1 ppm F) R* and dilute to 50.0 mL with *0.1 M hydrochloric acid*. To 20.0 mL of this solution add 20.0 mL of *total-ionic-strength-adjustment buffer R* and 3 mL of an 82 g/L solution of *anhydrous sodium acetate R*. Adjust to pH 5.2 with *ammonia R* and dilute to 50.0 mL with *distilled water R*.

Reference solution *Fluoride standard solution (10 ppm F) R*.

Indicator electrode Fluoride-selective.

Reference electrode Silver-silver chloride.

Carry out the measurements on the test solution, then add at least 3 quantities, each of 0.5 mL, of the reference solution, carrying out a measurement after each addition. Calculate the concentration of fluorides using the calibration curve, taking into account the addition of fluoride to the test solution.

Sulfates (*2.4.13*)

Maximum 0.5 per cent.

Dilute 1 mL of solution S to 25 mL with *distilled water R*.

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20*. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Arsenic	2
Lead	1

www.webofpharma.com

https://nhathuocngocanh.com/

Iron (*2.4.9*)

Maximum 400 ppm.

Dilute 0.5 mL of solution S to 10 mL with *water R*.

Acid-insoluble matter

Maximum 0.2 per cent.

Dissolve 5.0 g in a mixture of 10 mL of *hydrochloric acid R* and 30 mL of *water R*. Filter, wash the residue with *water R* and dry to constant mass at 100-105 °C. The residue weighs a maximum of 10 mg.

Loss on ignition

Maximum 8.0 per cent, determined on 1.000 g by ignition at 800 ± 50 °C for 30 min.

ASSAY

Dissolve 0.200 g in a mixture of 1 mL of *hydrochloric acid R1* and 5 mL of *water R*. Add 25.0 mL of *0.1 M sodium edetate* and dilute to 200 mL with *water R*. Adjust to about pH 10 with *concentrated ammonia R*. Add 10 mL of *ammonium chloride buffer solution pH 10.0 R* and a few milligrams of *mordant black 11 triturate R*. Titrate the excess sodium edetate with *0.1 M zinc sulfate* until the colour changes from blue to violet.

1 mL of *0.1 M sodium edetate* is equivalent to 4.008 mg of Ca.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for calcium phosphate is used as a filler in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*)

Bulk and tapped density (*2.9.34*)

Powder flow (*2.9.36*)

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Polystyrene Sulfonate

General Notices

Calcium Polystyrene Sulphonate

Action and use

Used in the treatment of hyperkalaemia.

DEFINITION

Calcium Polystyrene Sulfonate is a cation-exchange resin prepared in the calcium form containing not less than 6.5% w/w and not more than 9.5% w/w of calcium, calculated with reference to the dried substance. Each g exchanges not less than 1.3 mEq and not more than 2.0 mEq of potassium, calculated with reference to the dried substance.

CHARACTERISTICS

A cream to light brown, fine powder.

Practically insoluble in *water* and in *ethanol (96%)*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of calcium polystyrene sulfonate *(RS 037)*.

B. Yields reaction C characteristic of *calcium salts*, Appendix VI.

TESTS

Particle size

Not more than 1% w/w is retained on a 150-µm sieve, Appendix XVII B. Use 20 g and sieve for 5 minutes.

Potassium

Not more than 0.1% of K when determined by *atomic emission spectrophotometry*, Appendix II D, measuring at 766.5 nm and using a solution prepared in the following manner. To 1.1 g of the substance being examined add 5 mL of *hydrochloric acid*, heat to boiling, cool and add 10 mL of *water*. Filter, wash the filter and residue with *water* and dilute the filtrate and washings to 25 mL with *water*. Use *potassium standard solution (100 ppm K)*, suitably diluted with *water*, to prepare the standard solutions.

Sodium

Not more than 0.1% of Na when determined by *atomic emission spectrophotometry*, Appendix II D, measuring at 589.0 nm and using a solution prepared in the following manner. To 1.1 g of the substance being examined add 5 mL of *hydrochloric acid*, heat to boiling, cool

www.webofpharma.com

https://thuocngocanh.com/

and add 10 mL of *water*. Filter, wash the filter and residue with *water* and dilute the filtrate and washings to 25 mL with *water*. Use *sodium solution (200 ppm Na)*, suitably diluted with *water*, to prepare the standard solutions.

Arsenic

1 g dispersed in 25 mL of *water* complies with the *limit test for arsenic*, Appendix VII (1 ppm).

Styrene

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 g of the substance being examined with 10 mL of *acetone* for 30 minutes, centrifuge and use the supernatant liquid.

(2) 0.0001% w/v of *styrene* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to styrene is not greater than the area of the peak in the chromatogram obtained with solution (2) (1 ppm).

Potassium exchange capacity

To 3 g of the substance being examined in a dry 250 mL glass-stoppered flask add 100 mL of a solution containing 0.7455% w/v of *potassium chloride* and 0.4401% w/v of *potassium hydrogen carbonate* in *water* (solution A), stopper and shake for 15 minutes. Filter and dilute 2 mL of the filtrate to 1000 mL with *water*. Determine the concentration of unbound potassium in this solution by *atomic emission spectrophotometry*, Appendix II D, measuring at 766.5 nm and using solution A suitably diluted with *water*, to prepare the standard solutions. Calculate the potassium exchange capacity of the substance being examined in milliequivalents taking the concentration of potassium in solution A as 144 milliequivalents of K per litre.

Loss on drying

When dried at 70° at a pressure not exceeding 0.7 kPa for 16 hours, loses not more than 8.0% of its weight. Use 2 g.

Microbial contamination

www.webofpharma.com

https://thuvienthuocngocanh.com/

Carry out a quantitative evaluation for Enterobacteria and certain other Gram-negative bacteria, Appendix XVI B1. 0.01 g of the substance being examined gives a negative result, Table I (most probable number of bacteria per gram fewer than 10^2).

ASSAY

For calcium

Carefully heat 1 g in a platinum crucible until a white ash is obtained and dissolve in 10 mL of *2M hydrochloric acid* with the aid of heat. Transfer the resulting solution to a conical flask using 20 mL of *water*. Add 50 mL of *0.05M disodium edetate VS*, 20 mL of *ammonia buffer pH 10.9* and titrate the excess of disodium edetate with *0.02M zinc sulfate VS*, using a 0.5% w/v solution of *mordant black 11* in *ethanol (96%)* as indicator to a red purple end point. Each mL of *0.05M disodium edetate VS* is equivalent to 2.004 mg of Ca.

STORAGE

Calcium Polystyrene Sulfonate should be kept in an airtight container.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Stearate

General Notices

(Ph. Eur. monograph 0882)

1592-23-0

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of calcium salts of different fatty acids consisting mainly of stearic (octadecanoic) acid [$(C_{17}H_{35}COO)_2Ca$; M_r 607] and palmitic (hexadecanoic) acid [$(C_{15}H_{31}COO)_2Ca$; M_r 550.9] with minor proportions of other fatty acids.

Content

— *calcium*: 6.4 per cent to 7.4 per cent (A_r 40.08) (dried substance);

— *stearic acid in the fatty acid fraction*: minimum 40.0 per cent;

— *sum of stearic acid and palmitic acid in the fatty acid fraction*: minimum 90.0 per cent.

CHARACTERS

Appearance

Fine, white or almost white, crystalline powder.

Solubility

Practically insoluble in water and in ethanol (96 per cent).

IDENTIFICATION

First identification: C, D.

Second identification: A, B, D.

A. Freezing point (2.2.18): minimum 53 °C, for the residue obtained in the preparation of solution S (see Tests).

B. Acid value (2.5.1): 195 to 210.

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.200 g of the residue obtained in the preparation of solution S in 25 mL of the prescribed mixture of solvents.

C. Examine the chromatograms obtained in the test for fatty acid composition.

Results The retention times of the principal peaks in the chromatogram obtained with the test solution are approximately the same as those of the principal peaks in the chromatogram obtained with the reference solution.

D. Neutralise 5 mL of solution S to *red litmus paper R* using *strong sodium hydroxide solution R*. The solution gives reaction (b) of calcium (*2.3.1*).

TESTS

Solution S

To 5.0 g add 50 mL of *peroxide-free ether R*, 20 mL of *dilute nitric acid R* and 20 mL of *distilled water R*. Boil under a reflux condenser until dissolution is complete. Allow to cool. In a separating funnel, separate the aqueous layer and shake the ether layer with 2 quantities, each of 5 mL, of *distilled water R*. Combine the aqueous layers, wash with 15 mL of *peroxide-free ether R* and dilute the aqueous layer to 50 mL with *distilled water R* (solution S). Evaporate the ether layer to dryness and dry the residue at 100-105 °C. Keep the residue for identification tests A and B.

Acidity or alkalinity

To 1.0 g add 20 mL of *carbon dioxide-free water R* and boil for 1 min with continuous shaking. Cool and filter. To 10 mL of the filtrate add 0.05 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Chlorides (*2.4.4*)

Maximum 0.1 per cent.

Dilute 0.5 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.3 per cent.

Dilute 0.5 mL of solution S to 15 mL with *distilled water R*.

Loss on drying (*2.2.32*)

Maximum 6.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

www.webofpharma.com

https://thuocngocanh.com/

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

ASSAY

Calcium

To 0.500 g in a 250 mL conical flask add 50 mL of a mixture of equal volumes of *anhydrous ethanol R* and *butanol R*, 5 mL of *concentrated ammonia R*, 3 mL of *ammonium chloride buffer solution pH 10.0 R*, 30.0 mL of *0.1 M sodium edetate* and 15 mg of *mordant black 11 triturate R*. Heat to 45-50 °C until the solution is clear. Cool and titrate with *0.1 M zinc sulfate* until the colour changes from blue to violet. Carry out a blank titration.

1 mL of *0.1 M sodium edetate* is equivalent to 4.008 mg of Ca.

Composition of fatty acids

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution In a conical flask fitted with a reflux condenser, dissolve 0.10 g of the substance to be examined in 5 mL of *boron trifluoride-methanol solution R*. Boil under a reflux condenser for 10 min. Add 4 mL of *heptane R* through the condenser. Boil under a reflux condenser for 10 min. Allow to cool. Add 20 mL of *saturated sodium chloride solution R*. Shake and allow the layers to separate. Remove about 2 mL of the organic layer and dry over 0.2 g of *anhydrous sodium sulfate R*. Dilute 1.0 mL of the solution to 10.0 mL with *heptane R*.

Reference solution Prepare the reference solution in the same manner as the test solution using 50.0 mg of *palmitic acid CRS* and 50.0 mg of *stearic acid CRS* instead of calcium stearate.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.4 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 2	70
	2 - 36	70 → 240
	36 - 41	240

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Injection port		220
Detector		260

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to methyl stearate: methyl palmitate = about 0.9.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to methyl palmitate and methyl stearate.

Calculate the content of palmitic acid and stearic acid.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for calcium stearate used as a lubricant in tablets and capsules.

Particle-size distribution (2.9.31)

Specific surface area (2.9.26, Method I)

Determine the specific surface area in the P/P_o range of 0.05 to 0.15.

Sample outgassing 2 h at 40 °C.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Calcium Sulfate Dihydrate

General Notices

Calcium Sulphate

(Ph. Eur. monograph 0982)

$CaSO_4,2H_2O$ 172.2 *10101-41-4*

Action and use

Excipient.

Ph Eur

DEFINITION

Content

98.0 per cent to 102.0 per cent of $CaSO_4,2H_2O$.

CHARACTERS

Appearance

White or almost white fine powder.

Solubility

Very slightly soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Loss on ignition (see Tests).

B. Solution S (see Tests) gives reaction (a) of sulfates (*2.3.1*).

C. Solution S gives reaction (a) of calcium (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in 50 mL of a 10 per cent *V/V* solution of *hydrochloric acid R* by heating at 50 °C for 5 min. Allow to cool.

Acidity or alkalinity

www.webofpharma.com

https://thuocngocanh.com/

Shake 1.5 g with 15 mL of *carbon dioxide-free water R* for 5 min. Allow to stand for 5 min and filter. To 10 mL of the filtrate add 0.1 mL of *phenolphthalein solution R* and 0.25 mL of *0.01 M sodium hydroxide*. The solution is red. Add 0.30 mL of *0.01 M hydrochloric acid*. The solution is colourless. Add 0.2 mL of *methyl red solution R*. The solution is reddish-orange.

Chlorides (*2.4.4*)

Maximum 300 ppm.

Shake 0.5 g with 15 mL of *water R* for 5 min. Allow to stand for 15 min and filter. Dilute 5 mL of the filtrate to 15 mL with *water R*.

Iron (*2.4.9*)

Maximum 100 ppm.

To 0.25 g add a mixture of 5 mL of *hydrochloric acid R* and 20 mL of *water R*. Heat to boiling, cool and filter.

Loss on ignition

18.0 per cent to 22.0 per cent, determined on 1.000 g by ignition to constant mass at 800 ± 50 °C.

ASSAY

Dissolve 0.150 g in 120 mL of *water R*. Carry out the complexometric titration of calcium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 17.22 mg of $CaSO_4,2H_2O$.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for calcium sulfate dihydrate used as filler in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*)

Bulk and tapped density (*2.9.34*)

Powder flow (*2.9.36*)

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

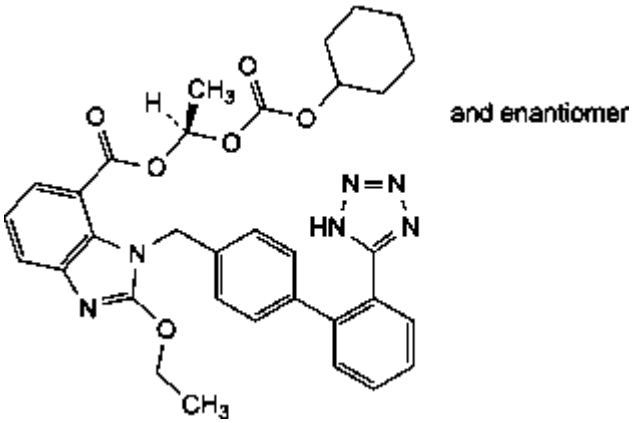
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Candesartan Cilexetil

General Notices

(Ph. Eur. monograph 2573)



$C_{33}H_{34}N_6O_6$ 611 *145040-37-5*

Action and use

Angiotensin II (AT1) receptor antagonist.

Preparation

Candesartan Tablets

Ph Eur

DEFINITION

(1*RS*)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in candesartan cilexetil should be avoided or limited as much as possible. For this reason, manufacturers of candesartan cilexetil for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-

www.webofpharma.com

https://thuocngocanh.com/

nitrosamine impurities in candesartan cilexetil. The general chapter 2.5.42. *N-Nitrosamines in active substances* is available to assist manufacturers.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride and slightly soluble in anhydrous ethanol.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *candesartan cilexetil CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture *water R*, *acetonitrile R* (40:60 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in 50.0 mL of the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *candesartan cilexetil for system suitability CRS* (containing impurities A, B and F) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (c) Dissolve 2.5 mg of *candesartan cilexetil for peak identification CRS* (containing impurities G and H) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: *glacial acetic acid R*, *water for chromatography R*, *acetonitrile R* (1:43:57 *V/V/V*);

— *mobile phase B*: *glacial acetic acid R*, *water for chromatography R*, *acetonitrile R* (1:10:90 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 33	100 → 0	0 → 100
33 - 40	0	100

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *candesartan cilexetil for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and F; use the chromatogram supplied with *candesartan cilexetil for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities G and H.

Relative retention With reference to candesartan cilexetil (retention time = about 11 min): impurity G = about 0.2; impurity A = about 0.4; impurity B = about 0.5; impurity F = about 2.0; impurity H = about 3.5.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurities A and B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurities A and G = 0.7; impurity H = 1.6;

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities F, G*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities A, H*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.32)

Maximum 0.3 per cent, determined on 60.0 mg.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

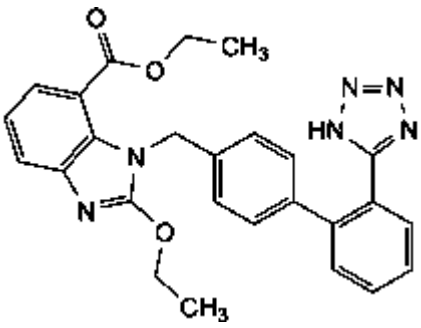
Dissolve 0.500 g in 60 mL of *glacial acetic acid R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20) at the 1st inflexion point.

1 mL of *0.1 M perchloric acid* is equivalent to 61.1 mg of $C_{33}H_{34}N_6O_6$.

IMPURITIES

Specified impurities *A, B, F, G, H.*

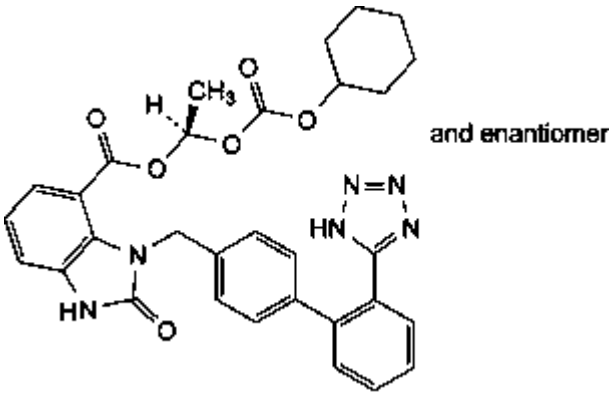
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, I.*



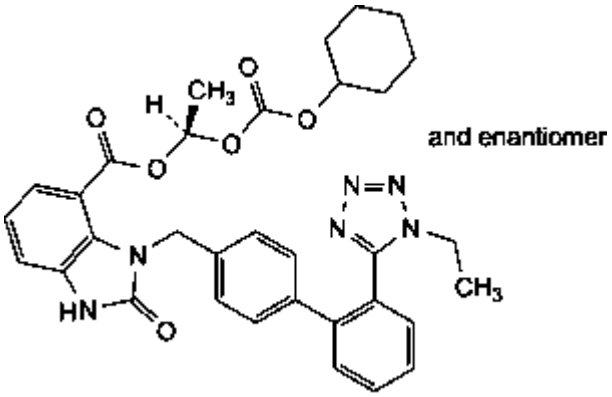
A. ethyl 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate,

www.webofpharma.com

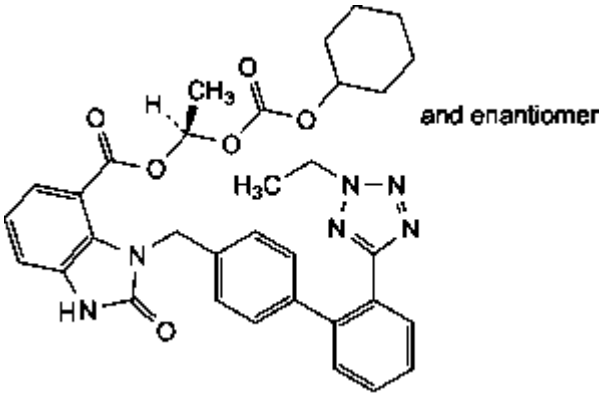
https://thuocngocanh.com/



B. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-oxo-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2,3-dihydro-1*H*-benzimidazole-4-carboxylate,



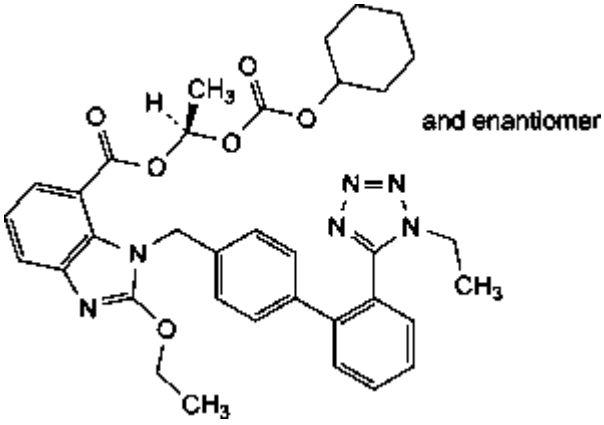
C. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 3-[[2′-(1-ethyl-1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate,



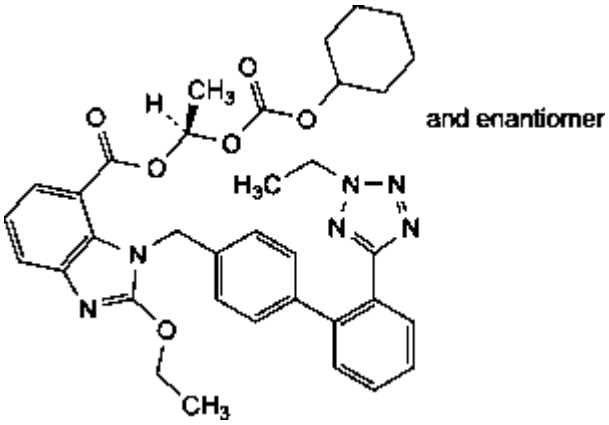
D. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 3-[[2′-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate,

www.webofpharma.com

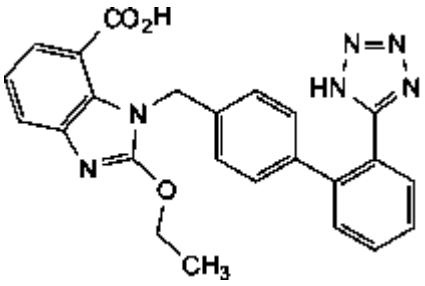
https://thuocngocanh.com/



E. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1-ethyl-1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate,



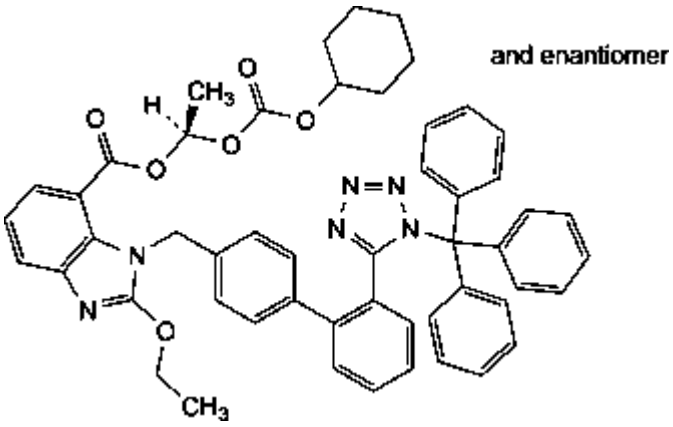
F. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate,



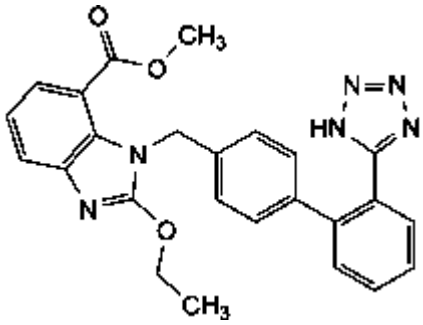
G. 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (candesartan),

www.webofpharma.com

https://thuocngocanh.com/



H. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (*N*-tritylcandesartan),



I. methyl 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Candesartan Tablets

General Notices

Action and use

Angiotensin II (AT_1) receptor antagonist.

DEFINITION

Candesartan Tablets contain Candesartan Cilexetil.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of candesartan cilexetil, $C_{33}H_{34}N_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 20 mg of Candesartan Cilexetil with 20 mL of *water* until the tablets have disintegrated and filter (a Whatman GF/C filter is suitable). Add the filter paper to 20 mL of *ethyl acetate*, mix with the aid of ultrasound and repeat the filtering process. Evaporate the filtrate to dryness under a stream of nitrogen. *The infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of candesartan cilexetil *(RS 494)*.

TESTS

Dissolution

For tablets containing 16 mg or less of candesartan cilexetil

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a solution containing 0.35% w/v of *polysorbate 20* in *phosphate buffer pH 6.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter (a Acrodisc GHP 25 0.45-µm filter is suitable). Dilute the filtered medium, if necessary, with sufficient dissolution medium to produce a solution expected to contain 0.00022% w/v of Candesartan Cilexetil.

(2) 0.00022% w/v of *candesartan cilexetil BPCRS* in the dissolution medium.

www.webofpharma.com

https://thatuocngocanh.com/

(3) 0.00022% w/v of *candesartan cilexetil for system suitability EPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Nova-Pak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 43 volumes of *water* and 57 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 4.0.

DETERMINATION OF CONTENT

Calculate the total content of candesartan cilexetil, $C_{33}H_{34}N_6O_6$, in the medium from the chromatograms obtained and using the declared content of $C_{33}H_{34}N_6O_6$ in *candesartan cilexetil BPCRS*.

LIMITS

The amount of candesartan cilexetil released is not less than 75% (Q) of the stated amount.

For tablets containing more than 16 mg of candesartan cilexetil

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a solution containing 0.70% w/v of *polysorbate 20* in *phosphate buffer pH 6.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter (a 0.45-µm Acrodisc GHP 25 filter is suitable). Dilute the filtered medium, if necessary, with sufficient dissolution medium to produce a solution expected to contain 0.00022% w/v of Candesartan Cilexetil.

(2) 0.00022% w/v of *candesartan cilexetil BPCRS* in the dissolution medium.

(3) 0.00022% w/v of *candesartan cilexetil for system suitability EPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under the Dissolution test for tablets containing 16 mg or less of candesartan cilexetil may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 4.0.

DETERMINATION OF CONTENT

Calculate the total content of candesartan cilexetil, $C_{33}H_{34}N_6O_6$, in the medium from the chromatograms obtained and using the declared content of $C_{33}H_{34}N_6O_6$ in *candesartan cilexetil BPCRS*.

LIMITS

The amount of candesartan cilexetil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 60% v/v *acetonitrile* prepared immediately before use.

(1) To a quantity of the powdered tablets containing 20 mg of Candesartan Cilexetil, add 80 mL of 60% v/v *acetonitrile* and mix with the aid of ultrasound. Add sufficient 60% v/v *acetonitrile* to produce 100 mL and filter (a 0.45-µm PTFE filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.05% w/v of *candesartan cilexetil for system suitability EPCRS*.
(4) 0.05% w/v of *candesartan cilexetil for peak identification EPCRS*.
(5) 0.05% w/v of *candesartan cilexetil impurity standard BPCRS*.
(6) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Nova-Pak C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.8 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *glacial acetic acid*, 43 volumes of *water* and 57 volumes of *acetonitrile*.

Mobile phase B 1 volume of *glacial acetic acid*, 10 volumes of *water* and 90 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic

www.webofpharma.com

https://thatuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-33	100→0	0→100	linear gradient
33-45	0	100	isocratic
45-47	0→100	100→0	linear gradient
47-55	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to candesartan cilexetil (retention time about 10 minutes) are: impurity G, about 0.2; impurity A, about 0.3; impurity B, about 0.5; impurity C, about 0.8; impurity D, about 1.2; impurity E, about 1.5; impurity F, about 2.0; impurity H, about 3.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 2.6, where *Hp* is the height above the baseline of the peak due to impurity D and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to candesartan cilexetil.

LIMITS

Use the chromatograms obtained with solutions (3) and (5) to identify the peaks due to impurities B, D and F.

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, G and H using solutions (3) and (4) and multiply the area of these peaks by the corresponding correction factors: impurity A, 0.7; impurity G, 0.7; impurity H, 1.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity C, D or E is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (6) (0.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1%).

For tablets containing 16 mg or less of candesartan cilexetil

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the sum of the areas of any *secondary peaks*, excluding the peak due to impurity B, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

For tablets containing more than 16 mg of candesartan cilexetil

www.webofpharma.com

https://thatuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of candesartan cilexetil must comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 60% v/v *acetonitrile*.

(1) Disperse one tablet in 25 mL of 60% v/v *acetonitrile* and mix with the aid of ultrasound for 10 minutes. Add sufficient 60% v/v *acetonitrile* to produce 50 mL and filter (a 0.45-µm PTFE filter is suitable). If necessary, dilute the filtrate with 60% v/v *acetonitrile* to produce a solution containing 0.0002% w/v of Candesartan Cilexetil.
(2) 0.0002 % w/v of *candesartan cilexetil BPCRS*.
(3) 0.015 % w/v of *candesartan cilexetil for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{33}H_{34}N_6O_6$ in each tablet using the declared content of $C_{33}H_{34}N_6O_6$ in *candesartan cilexetil BPCRS*.

ASSAY

For tablets containing 2 mg or less and/or less than 2% w/w of candesartan cilexetil

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing more than 2 mg and 2% w/w or more of candesartan cilexetil

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) To a quantity of the powdered tablets containing 20 mg of Candesartan Cilexetil, add 80 mL of 60% v/v *acetonitrile* and mix with the aid of ultrasound for 10 minutes. Dilute to 100 mL with 60% v/v *acetonitrile* and filter (a 0.45-µm PTFE filter is suitable). Add sufficient 60% v/v *acetonitrile* to the filtrate to produce a solution containing 0.002% w/v of Candesartan Cilexetil.
(2) 0.0002% w/v of *candesartan cilexetil BPCRS* in 60% v/v *acetonitrile*.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.015% w/v of *candesartan cilexetil for system suitability EPCRS* in 60% v/v *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{33}H_{34}N_6O_6$ in the tablets using the declared content of $C_{33}H_{34}N_6O_6$ in *candesartan cilexetil BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Candesartan Cilexetil.

© Crown Copyright 2022

www.webofpharma.com

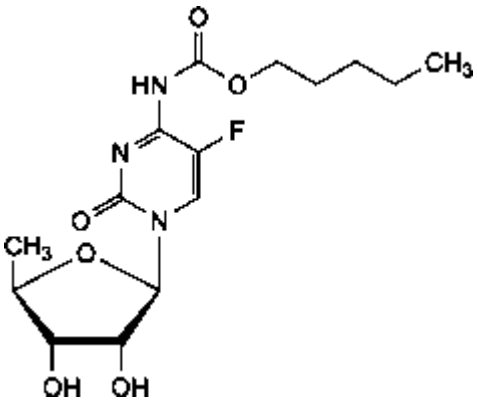
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Capecitabine

General Notices

(Ph. Eur. monograph 2762)



$C_{15}H_{22}FN_3O_6$ 359.3 *154361-50-9*

Action and use

Pyrimidine analogue; cytotoxic; treatment of colorectal cancer.

Preparation

Capecitabine Tablets

Ph Eur

DEFINITION

Pentyl [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Sparingly soluble in water, freely soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison capecitabine CRS.

TESTS

Specific optical rotation (2.2.7)

+ 96.0 to + 100.0 (anhydrous substance).

Dissolve 0.250 g in methanol R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 2-8 °C.*

Solvent mixture acetonitrile R, methanol R, water R (5:35:60 *V/V/V*).

Test solution Dissolve 60.0 mg of the substance to be examined in 80 mL of the solvent mixture, sonicate until dissolution is complete and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 60.0 mg of capecitabine CRS in 80 mL of the solvent mixture, sonicate until dissolution is complete and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 3 mg of capecitabine impurity A CRS, 3 mg of capecitabine impurity B CRS and 5 mg of capecitabine impurity D CRS in 80 mL of the solvent mixture, sonicate until dissolution is complete and dilute to 100.0 mL with the solvent mixture. Dilute 1 mL of the solution to 50 mL with the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, methanol R, 0.1 per cent *V/V* solution of glacial acetic acid R (5:35:60 *V/V/V*);

— *mobile phase B*: acetonitrile R, 0.1 per cent *V/V* solution of glacial acetic acid R, methanol R (5:15:80 *V/V/V*);

www.webofpharma.com

https://thuvienthuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 20	100 → 49	0 → 51
20 - 30	49	51

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and D.

Relative retention With reference to capecitabine (retention time = about 17 min): impurity A = about 0.18; impurity B = about 0.19; impurities D and E = about 0.95.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B; minimum 2.0 between the peaks due to impurity D and capecitabine.

Calculation of percentage contents:

— for each impurity, use the concentration of capecitabine in reference solution (b);

— *correction factor*: multiply the peak area of impurity B by 1.3.

Limits:

— *impurities A, B*: for each impurity, maximum 0.3 per cent;

— *sum of impurities D and E*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.03 per cent.

Water (*2.5.32*)

Maximum 0.3 per cent.

Inject 1.0 mL of a 0.200 g/mL solution of the substance to be examined in *methanol R*.

Sulfated ash (*2.4.14*)

www.webofpharma.com

https://thuvienthuocngocanh.com/

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

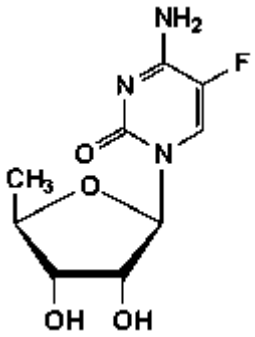
Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{15}H_{22}FN_3O_6$ taking into account the assigned content of *capecitabine CRS*.

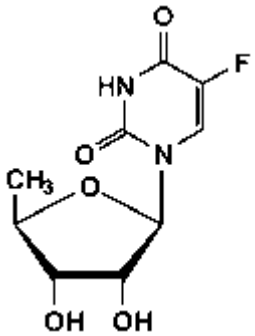
IMPURITIES

Specified impurities *A, B, D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, F, G.*



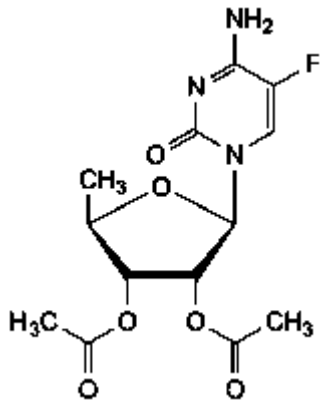
A. 4-amino-1-(5-deoxy-β-D-ribofuranosyl)-5-fluoropyrimidin-2(1*H*)-one (5'-deoxy-5-fluorocytidine),



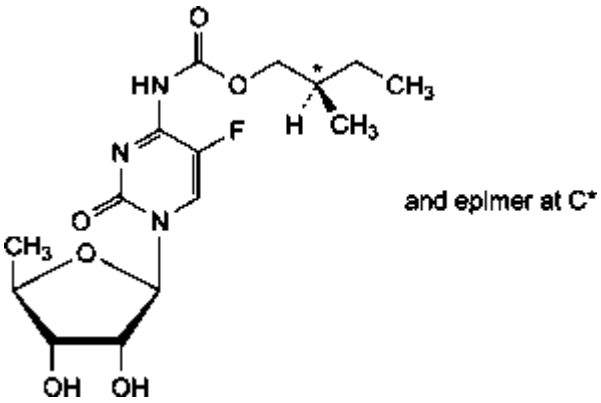
B. 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (5'-deoxy-5-fluorouridine),

www.webofpharma.com

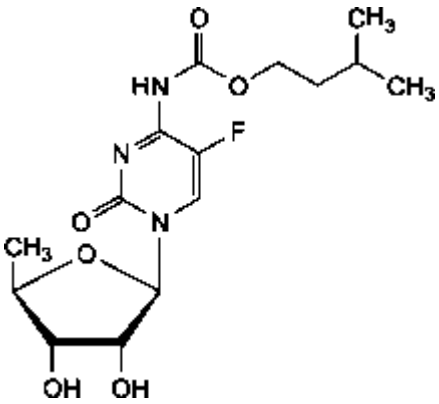
https://thuocngocanh.com/



C. 1-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-4-amino-5-fluoropyrimidin-2(1*H*)-one,



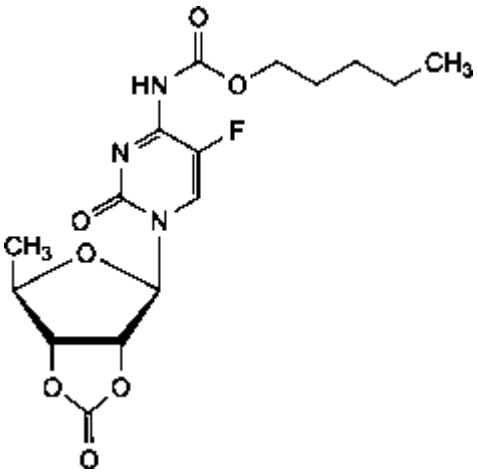
D. (2*RS*)-2-methylbutyl [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate,



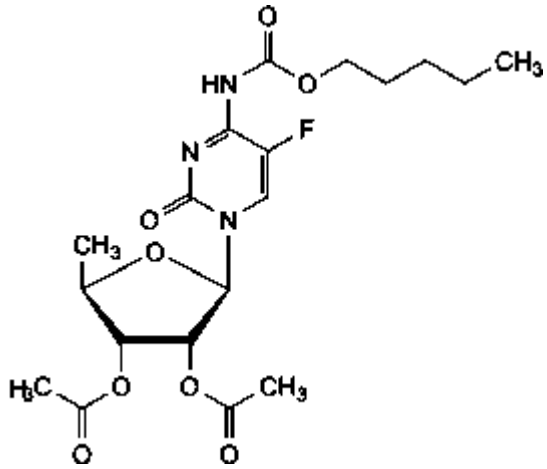
E. 3-methylbutyl [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate,

www.webofpharma.com

https://thuocngocanh.com/



F. pentyl [5-fluoro-1-[(3a*R*,4*R*,6*R*,6a*R*)-6-methyl-2-oxotetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate,



G. pentyl [1-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thatuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Capecitabine Tablets

General Notices

Action and use

Pyrimidine analogue; cytotoxic; treatment of cancer.

DEFINITION

Capecitabine Tablets contain Capecitabine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of capecitabine, $C_{15}H_{22}FN_3O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.05 g of Capecitabine with 4 mL of *ethanol* and filter. Evaporate the filtrate to dryness, under a stream of nitrogen, on a water bath at 65°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of *capecitabine BPCRS* treated in the same manner.

TESTS

Dissolution

Carry out the following procedure protected from light. Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 6.8*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the dissolution medium and filter. Use the filtered medium, diluted with *phosphate buffer pH 6.8*, if necessary, to produce a solution expected to contain 0.017% w/v of Capecitabine.

(2) 0.017% w/v of *capecitabine BPCRS* in *phosphate buffer pH 6.8*.

(3) 0.017% w/v of *capecitabine BPCRS* and 0.000025% w/v of *capecitabine impurity D EPCRS* in *phosphate buffer pH 6.8*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse XDB-C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 250 nm.

(f) Inject 40 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile*, 35 volumes of *methanol* and 60 volumes of a 0.1% v/v solution of *glacial acetic acid*.

Mobile phase B 5 volumes of *acetonitrile*, 80 volumes of *methanol* and 15 volumes of a 0.1% v/v solution of *glacial acetic acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-20	100→49	0→51	linear gradient
20-30	49	51	isocratic
30-32	49→100	51→0	linear gradient
32-40	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and capecitabine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{22}FN_3O_6$ in the medium using the declared content of $C_{15}H_{22}FN_3O_6$ in *capecitabine BPCRS*.

LIMITS

The amount of capecitabine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Prepare the solutions immediately before use.*

Solvent A 5 volumes of *acetonitrile*, 35 volumes of *methanol* and 60 volumes of *water*.

(1) Shake a quantity of powdered tablets containing 60 mg of Capecitabine with 80 mL of solvent A, dilute to 100 mL with the solvent A and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A.

(3) Dilut1 2 volume of solution (2) to 5 volumes with solvent A.

www.webofpharma.com

https://thuocngocanh.com/

(4) 0.06% w/v of *capecitabine BPCRS* and 0.0001% w/v each of *capecitabine impurity A EPCRS*, *capecitabine impurity B EPCRS* and *capecitabine impurity D EPCRS* in solvent A.

The chromatographic conditions described under Dissolution may be used with an injection volume of 10 µL.

When chromatograms are recorded under the prescribed conditions, the retention times relative to capecitabine (retention time, about 16 minutes) are: impurity A, about 0.16; impurity B, about 0.18; impurities D and E (co-elute), 0.94.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution* between the peaks due to impurity A and impurity B is at least 1.5;

the *resolution* between the peaks due to impurity D and capecitabine is at least 2.0.

LIMITS

Identify any peak corresponding to impurity B using the chromatogram obtained with solution (4) and multiply the peak area by the *correction factor* of 1.3.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A or impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any peak due to impurities D and E is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Prepare the solutions immediately before use.*

Solvent A 5 volumes of *acetonitrile*, 35 volumes of *methanol* and 60 volumes of *water*.

(1) Shake a quantity of powdered tablets containing 60 mg of Capecitabine with 80 mL of solvent A, dilute to 100 mL with the solvent A and filter.

(2) 0.06% w/v of *capecitabine BPCRS* in solvent A.

(3) 0.06% w/v of *capecitabine BPCRS* and 0.0001% w/v of *capecitabine impurity D EPCRS* in solvent A.

The chromatographic conditions described under Dissolution may be used with an injection volume of 10 µL.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and capecitabine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{22}FN_3O_6$ in the tablets using the declared content of $C_{15}H_{22}FN_3O_6$ in *capecitabine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Capecitabine*.

© Crown Copyright 2022

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Caprylocaproyl Macrogolglycerides

General Notices

(Ph. Eur. monograph 1184)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixtures of monoesters, diesters and triesters of glycerol and monoesters and diesters of macrogols with a mean relative molecular mass between 200 and 400.

They are obtained by partial alcoholysis of medium-chain triglycerides using macrogol, or by esterification of glycerol and macrogol with caprylic (octanoic) acid and capric (decanoic) acid, or by mixing glycerol esters and condensates of ethylene oxide with caprylic acid and capric acid. They may contain free macrogols.

CHARACTERS

Appearance

Pale-yellow, oily liquid.

Solubility

Dispersible in hot water, freely soluble in methylene chloride.

Density: about 1.0 at 20 °C.

Refractive index

About 1.4 at 20 °C.

IDENTIFICATION

A. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Application 50 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine B R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The chromatogram shows a spot due to triglycerides with an R_F value of about 0.9 (R_{st} 1) and spots due to 1,3-diglycerides (R_{st} 0.7), to 1,2-diglycerides (R_{st} 0.6), to monoglycerides (R_{st} 0.1) and to esters of macrogol (R_{st} 0).

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

TESTS

Viscosity (*2.2.9*)

Carry out the determination at 20 ± 0.5 °C.

Ethylene oxide units per molecule (nominal value)	Type of macrogol	Viscosity (mPa·s)
4	200	30 to 50
6	300	60 to 80
8	400	80 to 110

Acid value (*2.5.1*)

Maximum 2.0, determined on 2.0 g.

Hydroxyl value (*2.5.3, Method A*)

Use 1.0 g.

Ethylene oxide units per molecule (nominal value)	Type of macrogol	Hydroxyl value
4	200	80 to 120
6	300	140 to 180
8	400	170 to 205

Peroxide value (*2.5.5, Method A*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 6.0, determined on 2.0 g.

Saponification value (2.5.6)

Use 2.0 g.

Ethylene oxide units per molecule (nominal value)	Type of macrogol	Saponification value
4	200	265 to 285
6	300	170 to 190
8	400	85 to 105

Alkaline impurities

Introduce 5.0 g into a test-tube and carefully add a mixture, neutralised if necessary with *0.01 M hydrochloric acid* or with *0.01 M sodium hydroxide*, of 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*, 0.3 mL of *water R* and 10 mL of *ethanol (96 per cent) R*. Shake and allow to stand. Not more than 1.0 mL of *0.01 M hydrochloric acid* is required to change the colour of the upper layer to yellow.

Free glycerol

Maximum 5.0 per cent.

Dissolve 1.20 g in 25.0 mL of *methylene chloride R*. Heat if necessary. After cooling, add 100 mL of *water R*. Shake and add 25.0 mL of *periodic acetic acid solution R*. Shake and allow to stand for 30 min. Add 40 mL of a 75 g/L solution of *potassium iodide R*. Allow to stand for 1 min. Add 1 mL of *starch solution R*. Titrate the iodine with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 2.3 mg of glycerol.

Composition of fatty acids (2.4.22, Method A)

Composition of the fatty-acid fraction of the substance:

— *caproic acid*: maximum 2.0 per cent;

— *caprylic acid*: 50.0 per cent to 80.0 per cent;

— *capric acid*: 20.0 per cent to 50.0 per cent;

— *lauric acid*: maximum 3.0 per cent;

— *myristic acid*: maximum 1.0 per cent.

Ethylene oxide and dioxan (2.4.25)

Maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

www.webofpharma.com

https://thuocngocanh.com/

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g. Use a mixture of 30 volumes of *anhydrous methanol R* and 70 volumes of *methylene chloride R* as solvent.

Total ash (*2.4.16*)

Maximum 0.1 per cent.

LABELLING

The label states the type of macrogol used (mean relative molecular mass) or the number of ethylene oxide units per molecule (nominal value).

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for caprylocaproyl macrogolglycerides used as self-emulsifying agents and solubilisers.

Hydroxyl value

(see Tests).

Saponification value

(see Tests).

Composition of fatty acids

(see Tests).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Captopril Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Angiotensin-converting enzyme inhibitor.

DEFINITION

Captopril Oral Solution is a solution containing Captopril in a suitable flavoured vehicle. It is supplied as a ready-to-use solution or it is prepared by dissolving Captopril Powder for Oral Solution in the requisite volume of the vehicle provided just before issue for use.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate the oral solution also complies with the requirements stated under Unlicensed Medicines.

STORAGE

The oral solution should be stored at the temperature and used within the period stated on the label.

When supplied as a ready-to-use solution, the oral solution complies with the following requirements.

Content of captopril, $C_9H_{15}NO_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Add 10 mL of *dichloromethane* to a quantity of the oral solution containing 0.1 g of Captopril and shake gently (take care to avoid forming an emulsion). Remove the lower organic layer, repeat the extraction with two further 10-mL quantities of *dichloromethane*, combine the organic extracts and filter through *anhydrous sodium sulfate*. Mix 1 mL of the filtrate with 0.5 g of *potassium bromide*, dry at room temperature at a pressure of 2 kPa, grind to a uniform mixture and prepare a disc. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of captopril (*RS 038*).

TESTS

Captopril disulfide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the oral solution containing 25 mg of Captopril to 50 mL with *methanol* and mix.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

www.webofpharma.com

https://thietbiuocngocanh.com/

(3) Dissolve 5 mg of *captopril BPCRS* in 1 mL *methanol* and add 230 µL of 0.05M *iodine*. If the solution is not colourless, add 0.1M *sodium thiosulfate* dropwise until it becomes colourless, and dilute to 50 mL with *methanol* (generation of captopril disulfide). Further dilute 3 volumes to 20 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volume of *orthophosphoric acid*, 450 volumes of *water* and 550 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retention of captopril disulfide (impurity A) with reference to captopril (retention time about 4 minutes) is 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to captopril and captopril disulfide is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to captopril disulfide is not greater than three times the area of the peak in the chromatogram obtained with solution (2) (3%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the oral solution containing 25 mg of Captopril to 50 mL with mobile phase, mix and dilute 1 volume of the resulting solution to 5 volumes with the mobile phase.
(2) 0.01% w/v of *captopril BPCRS*.
(3) Dissolve 5 mg of *captopril BPCRS* in 1 mL of the mobile phase and add 230 µL of 0.05M *iodine*. If the solution is not colourless, add 0.1M *sodium thiosulfate* dropwise until it becomes colourless, and dilute to 50 mL (generation of captopril disulfide). Dilute 1 volume to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volume of *orthophosphoric acid*, 450 volumes of *water* and 550 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to captopril and captopril disulfide is at least 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_9H_{15}NO_3S$, weight in volume, using the declared content of $C_9H_{15}NO_3S$ in *captopril BPCRS*.

CAPTOPRIL POWDER FOR ORAL SOLUTION

DEFINITION

Captopril Powder for Oral Solution is a dry powder consisting of Captopril with or without excipients. It is supplied in a sealed container.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids. Where appropriate, the dry ingredients also comply with the requirements stated under Unlicensed Medicines.

Content of captopril, $C_9H_{15}NO_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of captopril (*RS 038*).

TESTS

Acidity

pH of a solution containing 2% w/v of Captopril, 2.0 to 2.6, Appendix V L.

Clarity of solution

A solution containing 2% w/v of Captopril in *carbon dioxide-free water* is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method II.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thatuocngocanh.com/

(1) Dissolve a quantity of the contents of the sealed container containing 50 mg of Captopril in the mobile phase and add sufficient mobile phase to produce 100 mL.

(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase.

(3) Dissolve a quantity of the mixed contents of the sealed containers containing 10 mg of Captopril in mobile phase, add 0.25 mL of 0.05 M *iodine* and sufficient mobile phase to produce 100 mL. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of Captopril.

MOBILE PHASE

0.5 volume of *orthophosphoric acid*, 500 volumes of *methanol* and 500 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three principal peaks and the *resolution* between the last two eluting principal peaks is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all such peaks is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and any peak with a retention time less than 1.4 minutes.

ASSAY

Mix the contents of 10 containers and dissolve a quantity of the mixed contents containing 0.15 g of Captopril in 30 mL of *water*. Titrate with 0.05M *iodine*, determining the end-point potentiometrically, Appendix VIII B, using a combined platinum electrode.

Each mL of 0.05M *iodine* is equivalent to 21.73 mg of $C_9H_{15}NO_3S$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Captopril Tablets

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Captopril Tablets contain Captopril.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of captopril, $C_9H_{15}NO_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a quantity of the powdered tablets containing 0.1 g of Captopril in 25 mL of *methanol* with the aid of ultrasound and filter. Mix 1 mL of the filtrate with 0.5 g of *potassium bromide*, dry at room temperature at 2 kPa, grind to a uniform mixture and prepare a disc. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of captopril *(RS 038)*.

TESTS

Captopril disulfide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Transfer a quantity of the powdered tablets containing 25 mg of Captopril to a centrifuge tube, add 50 mL of *methanol*, centrifuge for 15 minutes and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) Dissolve 5 mg of *captopril BPCRS* in 1 mL *methanol* and add 230 µL of 0.05M *iodine*. If the solution is not colourless, add 0.1M *sodium thiosulfate* dropwise until it becomes colourless, and dilute to 50 mL with *methanol* (generation of captopril disulfide). Further dilute 3 volumes to 20 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Ace C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

www.webofpharma.com

https://thatuocngocanh.com/

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.5 volume of *orthophosphoric acid*, 450 volumes of *water* and 550 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retention of captopril disulfide (impurity A) with reference to captopril (retention time about 4 minutes) is 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to captopril and captopril disulfide is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to captopril disulfide is not greater than three times the area of the peak in the chromatogram obtained with solution (2) (3%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Transfer a quantity of the powdered tablets containing 25 mg of Captopril to a centrifuge tube, add 25 mL of the mobile phase, mix with the aid of ultrasound for 15 minutes and centrifuge. Dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.

(2) 0.01% w/v of *captopril BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Captopril disulfide may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{15}NO_3S$ in the tablets using the declared content of $C_9H_{15}NO_3S$ in *captopril BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

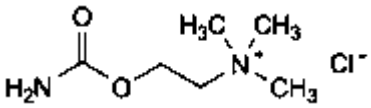
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Carbachol

General Notices

(Ph. Eur. monograph 1971)



$C_6H_{15}ClN_2O_2$ 182.7 *51-83-2*

Action and use

Cholinoceptor agonist.

Ph Eur

DEFINITION

2-(Carbamoyloxy)-*N,N,N*-trimethylethanaminium chloride.

Content

99.0 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline, hygroscopic powder.

Solubility

Very soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison carbachol CRS.

B. Examine the chromatograms obtained in the test for related substances.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. 0.5 mL of solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in carbon dioxide-free water R and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 2.0 mL of solution S, add 0.05 mL of methyl red mixed solution R. Not more than 0.2 mL of 0.01 M hydrochloric acid or 0.01 M sodium hydroxide is required to change the colour of the indicator.

Related substances

Thin-layer chromatography (2.2.27).

Prepare the solutions immediately before use.

Test solution (a) Dissolve 0.20 g of the substance to be examined in methanol R and dilute to 5.0 mL with the same solvent.

Test solution (b) Dilute 2.0 mL of test solution (a) to 20.0 mL with methanol R.

Reference solution (a) Dissolve 20 mg of carbachol CRS in methanol R and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 8 mg of choline chloride R and 8 mg of acetylcholine chloride CRS in methanol R and dilute to 10.0 mL with the same solvent. Dilute 5.0 mL to 10.0 mL with methanol R.

Plate cellulose for chromatography R as the coating substance.

Mobile phase water R, methanol R (10:90 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spray with *potassium iodobismuthate solution R3*.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated spots.

Limits In the chromatogram obtained with test solution (a):

— *any impurity*: any spot, apart from the principal spot, is not more intense than one or other of the 2 principal spots in the chromatogram obtained with reference solution (b) (1 per cent). Compare the spots with the spot of the most appropriate colour in the chromatogram obtained with reference solution (b).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g of the residue obtained in the test for loss on drying.

ASSAY

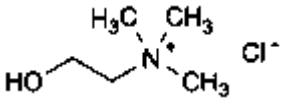
Dissolve 0.150 g in a mixture of 10 mL of *anhydrous acetic acid R* and 40 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*. Determine the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 18.27 mg of $C_6H_{15}ClN_2O_2$.

STORAGE

In an airtight container, protected from light.

IMPURITIES



A. 2-hydroxy-*N,N,N*-trimethylethanaminium chloride (choline chloride).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

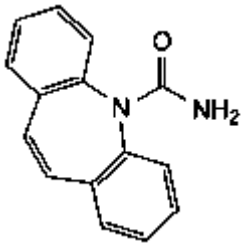
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbamazepine

General Notices

(Ph. Eur. monograph 0543)



$C_{15}H_{12}N_2O$ 236.3 *298-46-4*

Action and use

Antiepileptic.

Preparations

Carbamazepine Oral Suspension

Carbamazepine Tablets

Carbamazepine Chewable Tablets

Carbamazepine Prolonged-release Tablets

Ph Eur

DEFINITION

5*H*-Dibenzo[*b,f*]azepine-5-carboxamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and in ethanol (96 per cent).

It shows polymorphism (5.9). The acceptable crystalline form corresponds to *carbamazepine CRS*.

IDENTIFICATION

A. Melting point (2.2.14): 189 °C to 193 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *carbamazepine CRS*.

Preparation Examine the substances as discs without prior treatment.

TESTS

Acidity or alkalinity

To 1.0 g add 20 mL of *carbon dioxide-free water R*, shake for 15 min and filter. To 10 mL of the filtrate add 0.05 mL of *phenolphthalein solution R1* and 0.5 mL of *0.01 M sodium hydroxide*; the solution is red. Add 1.0 mL of *0.01 M hydrochloric acid*; the solution is colourless. Add 0.15 mL of *methyl red solution R*; the solution is red.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 60.0 mg of the substance to be examined in *methanol R* and dilute to 20.0 mL with the same solvent. Sonicate. Dilute 10.0 mL of this solution to 20.0 mL with *water R*.

Test solution (b) Dilute 10.0 mL of test solution (a) to 50.0 mL with a mixture of equal volumes of *methanol R* and *water R*.

Reference solution (a) Dissolve 7.5 mg of *carbamazepine CRS*, 7.5 mg of *carbamazepine impurity A CRS* and 7.5 mg of *iminodibenzyl R* (impurity E) in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 50.0 mL with a mixture of equal volumes of *methanol R* and *water R*.

Reference solution (b) Dissolve 60.0 mg of *carbamazepine CRS* in *methanol R* and dilute to 20.0 mL with the same solvent. Sonicate. Dilute 5.0 mL of this solution to 50.0 mL with a mixture of equal volumes of *methanol R* and *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cyanosilyl silica gel for chromatography R* (10 µm).

Mobile phase *tetrahydrofuran R*, *methanol R1*, *water for chromatography R* (3:12:85 *V/V/V*); to 1000 mL of this solution add 0.2 mL of *anhydrous formic acid R* and 0.5 mL of *triethylamine R*.

Flow rate 2.0 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (a) and reference solution (a).

Run time 8 times the retention time of carbamazepine.

Relative retention With reference to carbamazepine (retention time = about 10 min): impurity A = about 0.9; impurity E = about 3.5.

System suitability:

— *resolution*: minimum 1.7 between the peaks due to impurity A and carbamazepine in the chromatogram obtained with reference solution (a).

Limits:

— *impurities A, E*: for each impurity, not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: not more than the area of the peak due to carbamazepine in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the peak due to carbamazepine in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the peak due to carbamazepine in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (2.4.4)

Maximum 140 ppm.

Suspend 0.715 g in 20 mL of *water R* and boil for 10 min. Cool and dilute to 20 mL with *water R*. Filter through a membrane filter (nominal pore size 0.8 µm). Dilute 10 mL of the filtrate to 15 mL with *water R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (b).

System suitability:

www.webofpharma.com

https://thuocngocanh.com/

— *repeatability*: reference solution (b).

Calculate the percentage content of $C_{15}H_{12}N_2O$ from the declared content of *carbamazepine CRS*.

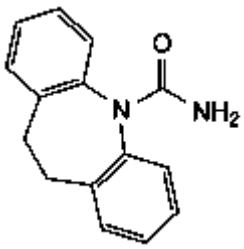
STORAGE

In an airtight container.

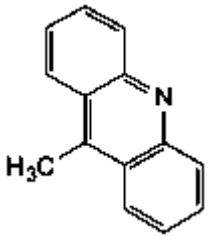
IMPURITIES

Specified impurities A, E.

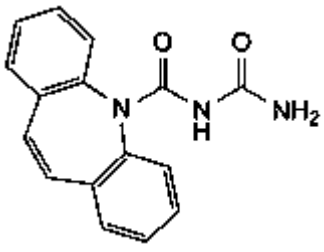
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, F, G.



A. 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide (10,11-dihydrocarbamazepine),



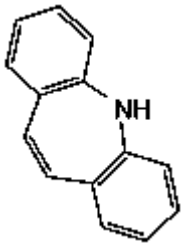
B. 9-methylacridine,



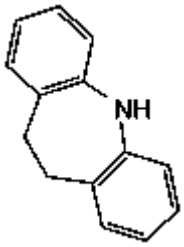
C. (5*H*-dibenzo[*b,f*]azepin-5-ylcarbonyl)urea (*N*-carbamoylcarbamazepine),

www.webofpharma.com

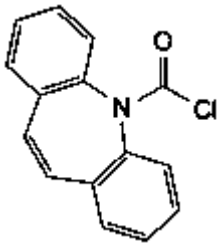
https://thuocngocanh.com/



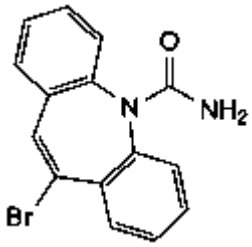
D. 5*H*-dibenzo[*b,f*]azepine (iminostilbene),



E. 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (iminodibenzyl),



F. 5*H*-dibenzo[*b,f*]azepine-5-carbonyl chloride (5-chlorocarbonyliminostilbene),



G. 10-bromo-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (10-bromocarbamazepine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbamazepine Chewable Tablets

General Notices

Chewable Carbamazepine Tablets

Carbamazepine Chewable Tablets from different manufacturers, whilst complying with the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Antiepileptic.

DEFINITION

Carbamazepine Chewable Tablets contain Carbamazepine.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Carbamazepine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of carbamazepine, $C_{15}H_{12}N_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Boil a quantity of the powdered tablets containing 0.2 g of Carbamazepine with 15 mL of *acetone*, filter the hot solution, wash the residue with two 5-mL quantities of hot *acetone*, cool in ice and evaporate the combined filtrates to dryness. The *infrared absorption spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of carbamazepine (*RS 406*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.3 g of Carbamazepine with 100 mL of *methanol* for 15 minutes. Dilute to 200 mL with *water*, mix and filter.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of solution (1) to 50 volumes with *methanol (50%)* and dilute 1 volume of the resulting solution to 10 volumes with *methanol (50%)*.

(3) Dilute 5 mg each of *carbamazepine BPCRS* and *carbamazepine impurity A EPCRS* in *methanol* and dilute to 50 mL with the same solvent. Dilute 1.0 mL of the resulting solution to 50 mL with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (10 µm) (Nucleosil CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 10 times the retention time of carbamazepine.

MOBILE PHASE

30 volumes of *tetrahydrofuran*, 120 volumes of *methanol* and 850 volumes of *water*, adding 0.2 volumes of *anhydrous formic acid* and 0.5 volumes of *triethylamine* to 1000 volumes of the solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to carbamazepine and carbamazepine impurity A is at least 1.7.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not more than 2.5 times the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.2 g of Carbamazepine with 100 mL of *methanol* for 15 minutes. Dilute to 200 mL with *water*, mix, filter and further dilute 1 volume of the filtrate to 5 volumes with *methanol (50%)*.

(2) Prepare a 0.2% w/v solution of *carbamazepine BPCRS* in *methanol* and dilute 1 volume of this solution to 2 volumes with *water*. Dilute 1 volume of the resulting solution to 5 volumes with *methanol (50%)*.

(3) 5 mg each of *carbamazepine BPCRS* and *carbamazepine impurity A EPCRS* in *methanol* and dilute to 50 mL with the same solvent. Dilute 1.0 mL of the resulting solution to 50 mL with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used, with the exception of the run time.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to carbamazepine and carbamazepine impurity A is at least 1.7.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{12}N_2O$, in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{12}N_2O$ in *carbamazepine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Carbamazepine.

© Crown Copyright 2022

www.webofpharma.com

https://thatluocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbamazepine Oral Suspension

General Notices

Carbamazepine Oral Suspensions from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable, unless justified and authorised.

Action and use

Antiepileptic.

DEFINITION

Carbamazepine Oral Suspension is a suspension of Carbamazepine in a suitable vehicle.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Carbamazepine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of carbamazepine, $C_{15}H_{12}N_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the oral suspension containing 100 mg of Carbamazepine add 20 mL of 0.1M *sodium hydroxide* and extract with 3 successive 20-mL quantities of *dichloromethane*.Dry the combined extracts over *anhydrous sodium sulfate* and evaporate the *dichloromethane*.The *infrared absorption spectrum* of the residue, is concordant with the *reference spectrum* of carbamazepine (*RS 406*).

TESTS

Acidity

pH, 3.5 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake, with the aid of ultrasound, a quantity of the oral suspension containing 0.2 g of Carbamazepine with 50 mL of *methanol*, cool and dilute to 100 mL with *water*.Centrifuge 10 mL of the solution, transfer 5 mL of the supernatant liquid to a 10-mL volumetric flask and

www.webofpharma.com

https://thatuocngocanh.com/

dilute to volume with *methanol (50%)*.

(2) Dilute 1 volume of solution (1) to 50 volumes with *methanol (50%)* and dilute 1 volume of the resulting solution to 10 volumes with *methanol (50%)*.

(3) Dilute 5 mg each of *carbamazepine BPCRS* and *carbamazepine impurity A EPCRS* in *methanol (50%)* and dilute to 50 mL with the same solvent. Dilute 1.0 mL of the resulting solution to 50 mL with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (10 µm) (Nucleosil CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

(g) Inject solution (1) and allow the chromatography to proceed for 10 times the retention time of carbamazepine.

MOBILE PHASE

30 volumes of *tetrahydrofuran*, 120 volumes of *methanol* and 850 volumes of *water*, adding 0.2 volumes of *anhydrous formic acid* and 0.5 volumes of *trimethylamine* to 1000 volumes of the solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to carbamazepine and carbamazepine impurity A is at least 1.7.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not more than 2.5 times the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a weighed quantity of the oral suspension containing 0.2 g of Carbamazepine with 100 mL of *methanol* for 15 minutes. Dilute to 200 mL with *water*, mix, filter and further dilute 1 volume of the filtrate to 5 volumes with *methanol (50%)*.

(2) Prepare a 0.2% w/v solution of *carbamazepine BPCRS* in *methanol* and dilute 1 volume of this solution to 2 volumes with *water*. Dilute 1 volume of the resulting solution to 5 volumes with *methanol (50%)*.

(3) 5 mg each of *carbamazepine BPCRS* and *carbamazepine impurity A EPCRS* in *methanol (50%)* and dilute to 50 mL with the same solvent. Dilute 1.0 mL of the resulting solution to 50 mL with *methanol (50%)*.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to carbamazepine and carbamazepine impurity A is at least 1.7.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{15}H_{12}N_2O$, weight in volume, using the declared content of $C_{15}H_{12}N_2O$ in *carbamazepine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Carbamazepine.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbamazepine Prolonged-release Tablets

General Notices

Prolonged-release Carbamazepine Tablets

Carbamazepine Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Antiepileptic.

DEFINITION

Carbamazepine Prolonged-release Tablets contain Carbamazepine. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Carbamazepine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of carbamazepine, $C_{15}H_{12}N_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Boil a quantity of the powdered tablets containing 0.2 g of Carbamazepine with 15 mL of *acetone*, filter the hot solution, wash the residue with two 5-mL quantities of hot *acetone*, cool in ice and evaporate the combined filtrates to dryness. The *infrared absorption spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of carbamazepine (*RS 406*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.3 g of Carbamazepine with 100 mL of *methanol* for 15 minutes. Dilute to 200 mL with *water*, mix and filter.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (50%)* and dilute 1 volume of the resulting solution to 5 volumes with the same solvent.

(3) Dissolve 7.5 mg each of *carbamazepine BPCRS* and *carbamazepine impurity A EPCRS* in *methanol* and dilute to 100 mL with the same solvent. Dilute 1.0 mL of the resulting solution to 50 mL with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (10 µm) (Nucleosil 10 CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 10 times the retention time of carbamazepine.

MOBILE PHASE

30 volumes of *tetrahydrofuran*, 120 volumes of *methanol* and 850 volumes of *water*, adding 0.2 volumes of *anhydrous formic acid* and 0.5 volume of *triethylamine* to 1000 volumes of the solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to carbamazepine and carbamazepine impurity A is at least 1.7.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.3 g of Carbamazepine with 100 mL of *methanol* for 15 minutes. Dilute to 200 mL with *water*, mix, filter and further dilute 1 volume of the filtrate to 5 volumes with *methanol (50%)*.

(2) Prepare a 0.3% w/v solution of *carbamazepine BPCRS* in *methanol* and dilute 1 volume of this solution to 2 volumes with *water*. Dilute 1 volume of the resulting solution to 5 volumes with *methanol (50%)*.

(3) Dissolve 7.5 mg each of *carbamazepine BPCRS* and *carbamazepine impurity A EPCRS* in *methanol* and dilute to 100 mL with the same solvent. Dilute 1.0 mL of the resulting solution to 50 mL with *methanol (50%)*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used, with the exception of the run time.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to carbamazepine and carbamazepine impurity A is at least 1.7.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{12}N_2O$ in the tablets using the declared content of $C_{15}H_{12}N_2O$ in *carbamazepine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Carbamazepine.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbamazepine Tablets

General Notices

Carbamazepine Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Antiepileptic.

DEFINITION

Carbamazepine Tablets contain Carbamazepine.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Carbamazepine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of carbamazepine, $C_{15}H_{12}N_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Boil a quantity of the powdered tablets containing 0.2 g of Carbamazepine with 15 mL of *acetone*, filter the hot solution, wash the residue with two 5-mL quantities of hot *acetone*, cool in ice and evaporate the combined filtrates to dryness. The *infrared absorption spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of carbamazepine (*RS 406*).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.3 g of Carbamazepine with 100 mL of *methanol* for 15 minutes. Dilute to 200 mL with *water*, mix and filter.

(2) Dilute 1 volume of solution (1) to 500 volumes with *methanol (50%)*.

(3) Dissolve 7.5 mg each of *carbamazepine BPCRS* and *carbamazepine impurity A EPCRS* in *methanol* and dilute to 100 mL with the same solvent. Dilute 1.0 mL of the resulting solution to 50 mL with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (10 µm) (Nucleosil 10 CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 10 times the retention time of carbamazepine.

MOBILE PHASE

30 volumes of *tetrahydrofuran*, 120 volumes of *methanol* and 850 volumes of *water*, adding 0.2 volume of *anhydrous formic acid* and 0.5 volume of *triethylamine* to 1000 volumes of the solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to carbamazepine and carbamazepine impurity A is at least 1.7.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the peak due to carbamazepine in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.3 g of Carbamazepine with 100 mL of *methanol* for 15 minutes. Dilute to 200 mL with *water*, mix, filter and further dilute 1 volume of the filtrate to 5 volumes with *methanol (50%)*.

(2) 0.03% w/v of *carbamazepine BPCRS* in *methanol (50%)*.

(3) Dissolve 7.5 mg each of *carbamazepine BPCRS* and *carbamazepine impurity A EPCRS* in *methanol* and dilute to 100 mL with the same solvent. Dilute 1.0 mL of the resulting solution to 50 mL with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used, with the exception of the run time.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to carbamazepine and carbamazepine impurity A is at least 1.7.

www.webofpharma.com

https://thuviendhatuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{12}N_2O$ in the tablets using the declared content of $C_{15}H_{12}N_2O$ in *carbamazepine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Carbamazepine.

© Crown Copyright 2022

www.webofpharma.com

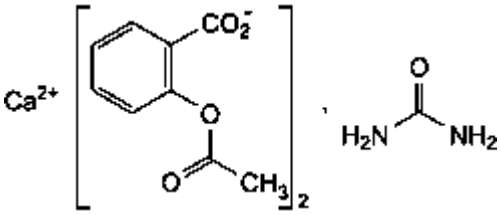
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbasalate Calcium

General Notices

(Ph. Eur. monograph 1185)



$C_{19}H_{18}CaN_2O_9$ 458.4 *5749-67-7*

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

Equimolecular compound of calcium di[2-(acetyloxy)benzoate] and urea.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in dimethylformamide, practically insoluble in acetone and in anhydrous methanol.

Protect the substance from moisture during handling. Examination in aqueous solutions has to be performed immediately after preparation.

IDENTIFICATION

First identification: B, E.

www.webofpharma.com

https://nhathuocngocanh.com/

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.250 g in water R and dilute to 100.0 mL with the same solvent. To 1.0 mL of the solution add 75 mL of water R and 5 mL of dilute hydrochloric acid R, mix and dilute to 100.0 mL with water R. Examine immediately.

Spectral range 220-350 nm.

Absorption maxima At 228 nm and 276 nm.

Specific absorbance at the absorption maxima:

— at 228 nm: 363 to 379,

— at 276 nm: 49 to 53.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison Ph. Eur. reference spectrum of carbasalate calcium.

C. Dissolve 0.1 g in 10 mL of water R, boil for 2 min and cool. The solution gives reaction (a) of salicylates (2.3.1).

D. Heat 0.2 g with 0.2 g of sodium hydroxide R; a yellow or yellowish-brown colour is produced and the vapour turns red litmus paper R blue.

E. It gives reaction (a) of calcium (2.3.1).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and is colourless (2.2.2, Method II).

Dissolve 2.5 g in 50 mL of water R.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture phosphoric acid R, methanol R, acetonitrile for chromatography R (0.5:8:92 *V/V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in 5 mL of the solvent mixture, sonicate for 15 min and dilute to 10.0 mL with the solvent mixture. Filter the solution through a membrane filter (nominal pore size 0.45 µm).

Reference solution (a) Dissolve 10.0 mg of salicylic acid CRS (impurity C) in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of carbasalate impurity B CRS in 20.0 mL of the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dilute 1.0 mL of the test solution to 10.0 mL with the solvent mixture. Mix 1.0 mL of this solution with 5.0 mL of reference solution (a), add 1.0 mL of reference solution (c) and dilute to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *phosphoric acid R*, *acetonitrile for chromatography R*, *water R* (0.5:40:60 *V/V/V*).

Flow rate 1.8 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL of the test solution and reference solutions (b) and (d).

Run time 8 times the retention time of acetylsalicylic acid.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B and C.

Relative retention With reference to acetylsalicylic acid (retention time = about 2 min): impurity C = about 1.3; impurity B = about 2.5.

System suitability Reference solution (d):

— *resolution*: minimum 5.0 between the peaks due to acetylsalicylic acid and impurity C.

Limits:

— *impurity C*: not more than 5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity B*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.03 per cent).

Sodium

Maximum 0.1 per cent.

Atomic emission spectrometry (*2.2.22, Method I*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 1.0 g in 500.0 mL of *water R*.

Water (*2.5.12*)

Maximum 0.1 per cent, determined on 1.000 g. Use a mixture of 15 mL of *anhydrous methanol R* and 15 mL of *dimethylformamide R* as the solvent.

ASSAY

In a flask with a ground-glass stopper, dissolve 0.400 g in 25 mL of *water R*. Add 25.0 mL of *0.1 M sodium hydroxide*. Close the flask and allow to stand for 2 h. Titrate with *0.1 M hydrochloric acid*, using 0.2 mL of *phenolphthalein solution R*. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 22.92 mg of $C_{19}H_{18}CaN_2O_9$.

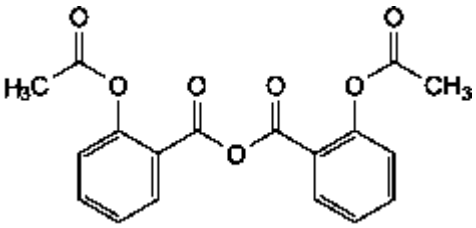
STORAGE

In an airtight container.

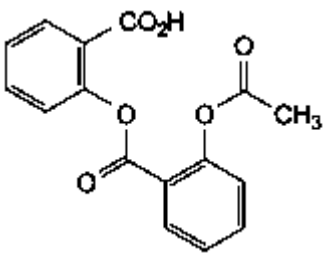
IMPURITIES

Specified impurities *B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D.*



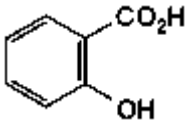
A. 2-(acetyloxy)benzoic anhydride,



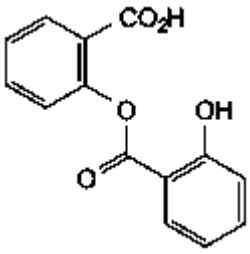
B. 2-[[2-(acetyloxy)benzoyl]oxy]benzoic acid (acetylsalicylsalicylic acid),

www.webofpharma.com

https://thuvienthuocngocanh.com/



C. 2-hydroxybenzenecarboxylic acid (salicylic acid),



D. 2-[(2-hydroxybenzoyl)oxy]benzoic acid (salicylsalicylic acid).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

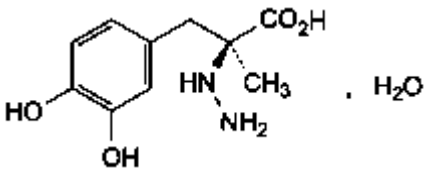
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbidopa

General Notices

(Ph. Eur. monograph 0755)



$C_{10}H_{14}N_2O_4,H_2O$ 244.2 *38821-49-7*

Action and use

Dopa decarboxylase inhibitor.

Preparation

Co-careldopa Tablets

Ph Eur

DEFINITION

(2*S*)-3-(3,4-Dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of mineral acids.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, C.

Second identification: A, B, D, E.

A. Specific optical rotation (see Tests).

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50 mg in an 8.5 g/L solution of *hydrochloric acid R* in *methanol R* and dilute to 100.0 mL with the same solution. Dilute 10.0 mL of this solution to 100.0 mL with an 8.5 g/L solution of *hydrochloric acid R* in *methanol R*.

Spectral range 230-350 nm.

Absorption maximum At 283 nm.

Specific absorbance at the absorption maximum 135 to 150 (dried substance).

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *carbidopa CRS*.

D. Shake vigorously about 5 mg with 10 mL of *water R* for 1 min and add 0.3 mL of *ferric chloride solution R2*. An intense green colour is produced, which quickly changes to reddish-brown.

E. Suspend about 20 mg in 5 mL of *water R* and add 5 mL of *cupri-tartaric solution R*. On heating, the colour of the solution changes to dark brown and a red precipitate is formed.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 or B_6 (2.2.2, Method II).

Dissolve 0.25 g in 25 mL of *1 M hydrochloric acid*.

Specific optical rotation (2.2.7)

-26.5 to -22.5 (dried substance).

Using an ultrasonic bath, dissolve completely 0.250 g in *aluminium chloride solution R* and dilute to 25.0 mL with the same solution.

Hydrazine

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.50 g in *dilute hydrochloric acid R* and dilute to 2.0 mL with the same acid.

Test solution (b) Place 25 g of *strongly basic anion-exchange resin R* into each of 2 conical flasks with ground-glass stoppers. To each, add 150 mL of *carbon dioxide-free water R* and shake from time to time during 30 min. Decant the liquid from both flasks and repeat the process with further quantities, each of 150 mL, of *carbon dioxide-free water R*.

www.webofpharma.com

https://thuocngocanh.com/

Take two 100 mL measuring cylinders 3.5-4.5 cm in internal diameter and label these A and B. Into cylinder A, transfer as completely as possible the resin from 1 conical flask using 60 mL of *carbon dioxide-free water R*; into cylinder B, transfer the 2nd quantity of resin, this time using 20 mL of *carbon dioxide-free water R*.

Into each cylinder, insert a gas-inlet tube, the end of which has an internal diameter of 2-3 mm and which reaches almost to the bottom of the cylinder. Pass a rapid stream of *nitrogen for chromatography R* through each mixture so that homogeneous suspensions are formed. After 30 min, without interrupting the gas flow, add 1.0 mL of test solution (a) to cylinder A; after 1 min stop the gas flow into cylinder A and transfer the contents, through a moistened filter paper, into cylinder B. After 1 min, stop the gas flow to cylinder B and pour the solution immediately through a moistened filter paper into a freshly prepared mixture of 1 mL of a 200 g/L solution of *salicylaldehyde R* in *methanol R* and 20 mL of *phosphate buffer solution pH 5.5 R* in a conical flask; shake thoroughly for 1 min and heat in a water-bath at 60 °C for 15 min. The liquid becomes clear. Allow to cool, add 2.0 mL of *toluene R* and shake vigorously for 2 min. Transfer the mixture into a centrifuge tube and centrifuge.

Separate the toluene layer in a 100 mL separating funnel and shake vigorously with 2 quantities, each of 20 mL, of a 200 g/L solution of *sodium metabisulfite R* and finally with 2 quantities, each of 50 mL, of *water R*. Separate the toluene layer.

Reference solution (a) Dissolve 10 mg of *hydrazine sulfate R* in *dilute hydrochloric acid R* and dilute to 50 mL with the same acid. Dilute 1.0 mL of this solution to 10.0 mL with *dilute hydrochloric acid R*.

Reference solution (b) Prepare the solution at the same time and in the same manner as described for test solution (b) using 1.0 mL of reference solution (a) instead of 1.0 mL of test solution (a).

Plate *TLC silanised silica gel plate R*.

Mobile phase *water R*, *methanol R* (10:20 *V/V*).

Application 10 µL of test solution (b) and reference solution (b).

Development Over 1/2 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 365 nm.

Limit:

— *hydrazine*: any spot showing a yellow fluorescence is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (20 ppm).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Buffer solution Dissolve 6.9 g of *sodium dihydrogen phosphate monohydrate R* in 900 mL of *water for chromatography R*, adjust to pH 2.2 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase, add 20 µL of *hydrochloric acid R* and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of *carbidopa for system suitability CRS* (containing impurities A, D, E, I and J) in the mobile phase, add 4 µL of *hydrochloric acid R* and dilute to 2.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *carbidopa impurity mixture CRS* (impurities F and H) in 1.0 mL of reference solution (b).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 25 °C.

Mobile phase *ethanol (96 per cent) R*, buffer solution (7:93 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 6 times the retention time of carbidopa.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, D + E, F, H, I and J.

Relative retention With reference to carbidopa (retention time = about 3 min): impurity A = about 0.9; impurities D and E = about 1.9; impurity H = about 2.5; impurity I = about 3.7; impurity J = about 4.0; impurity F = about 4.4.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity A and carbidopa in the chromatogram obtained with reference solution (b); minimum 1.5 between the peaks due to impurities I and J in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 30 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurities D and E = 1.5; impurity I = 1.5; impurity J = 1.5;

— for each impurity, use the concentration of carbidopa in reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity J*: maximum 0.25 per cent;

— *sum of impurities D and E*: maximum 0.2 per cent;

— *impurities F, H, I*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

6.9 per cent to 7.9 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g with gentle heating in 75 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 22.62 mg of $C_{10}H_{14}N_2O_4$.

STORAGE

Protected from light.

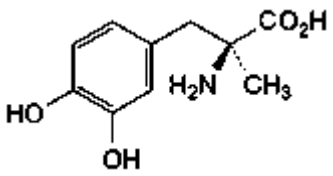
IMPURITIES

Specified impurities A, D, E, F, H, I, J.

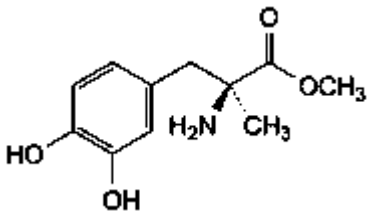
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, G.

www.webofpharma.com

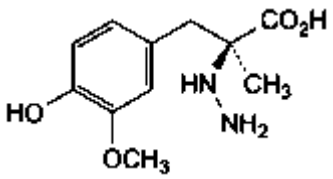
https://thuocngocanh.com/



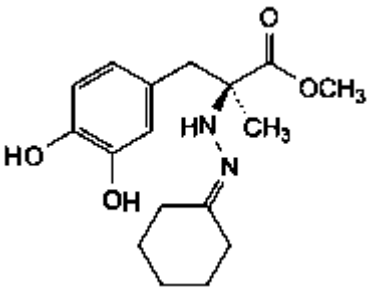
A. (2*S*)-2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid (L-methyldopa),



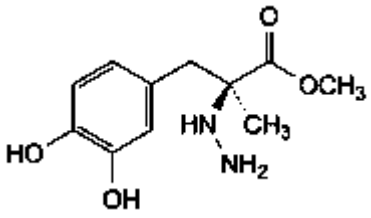
B. methyl (2*S*)-2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoate,



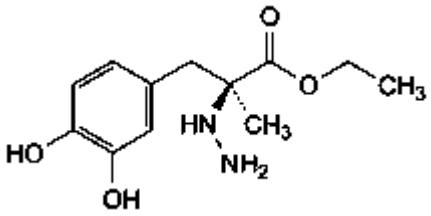
C. (2*S*)-2-hydrazino-3-(4-hydroxy-3-methoxyphenyl)-2-methylpropanoic acid (3-*O*-methylcarbidopa),



D. methyl (2*S*)-2-(2-cyclohexylidenehydrazino)-3-(3,4-dihydroxyphenyl)-2-methylpropanoate,



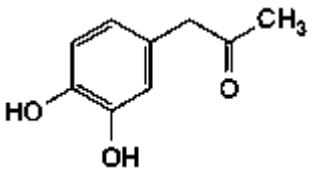
E. methyl (2*S*)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoate,



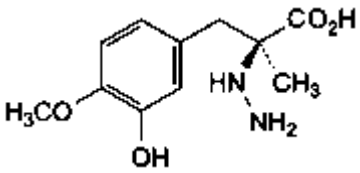
www.webofpharma.com

https://thuocngocanh.com/

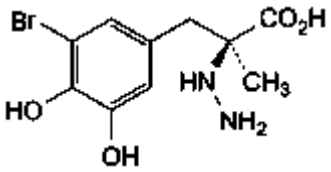
F. ethyl (2*S*)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoate,



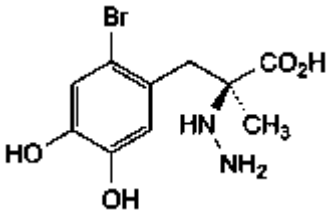
G. 1-(3,4-dihydroxyphenyl)propan-2-one,



H. (2*S*)-2-hydrazino-3-(3-hydroxy-4-methoxyphenyl)-2-methylpropanoic acid,



I. (2*S*)-3-(3-bromo-4,5-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid,



J. (2*S*)-3-(2-bromo-4,5-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

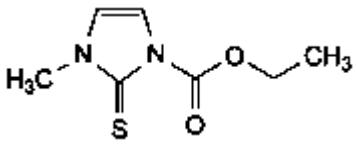
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbimazole

General Notices

(Ph. Eur. monograph 0884)



$C_7H_{10}N_2O_2S$ 186.2 *22232-54-8*

Action and use

Thionamide antithyroid drug.

Preparation

Carbimazole Tablets

Ph Eur

DEFINITION

Ethyl 3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazole-1-carboxylate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Slightly soluble in water, soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, C, D.

A. Melting point (2.2.14): 122 °C to 125 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison carbimazole CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methylene chloride R and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 10 mg of carbimazole CRS in methylene chloride R and dilute to 10.0 mL with the same solvent.

Plate TLC silica gel F_{254} plate R.

Mobile phase acetone R, methylene chloride R (20:80 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air for 30 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in a mixture of 0.05 mL of dilute hydrochloric acid R and 50 mL of water R. Add 1 mL of potassium iodobismuthate solution R. A red precipitate is formed.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture acetonitrile R, water R (20:80 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of thiamazole CRS (impurity A) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Mix 1 mL of the solution with 2 mL of the test solution and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5.0 mg of thiamazole CRS (impurity A) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 25.0 mg of *carbimazole CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *water R* (10:90 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a), (b) and (c).

Run time 1.5 times the retention time of carbimazole.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to carbimazole (retention time = about 6 min): impurity A = about 0.2.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity A and carbimazole.

Limits:

— *impurity A*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: maximum 0.6 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator at a pressure not exceeding 0.7 kPa for 24 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

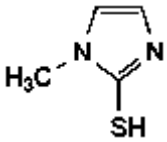
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (d).

Calculate the percentage content of $C_7H_{10}N_2O_2S$ taking into account the assigned content of *carbimazole CRS*.

IMPURITIES

Specified impurities *A*.



A. 1-methyl-1*H*-imidazole-2-thiol (thiamazole).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thatuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbimazole Tablets

General Notices

Action and use

Thionamide antithyroid drug.

DEFINITION

Carbimazole Tablets contain Carbimazole.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of carbimazole, $C_7H_{10}N_2O_2S$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 50 mg of Carbimazole with two 5-mL quantities of *dichloromethane*. Combine the dichloromethane extracts, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum*, Appendix II A, of the residue after drying at 60° at a pressure not exceeding 0.7 kPa for 30 minutes is concordant with the *reference spectrum* of carbimazole *(RS 042)*.

Thiamazole and other related substances

Carry out the test protected from light and prepare the solutions immediately before use.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 20 mg of Carbimazole in 10 mL of *acetonitrile* with the aid of ultrasound for 5 minutes, filter through a nylon syringe, filter and dilute 1 volume of the filtrate to 20 volumes with *water*.

(2) Dilute 1 volume of solution (1) to 200 volumes with mobile phase A.

(3) 0.00025% w/v of *thiamazole* in mobile phase A.

(4) 0.002% w/v of *carbimazole BPCRS* and 0.0001% w/v of *thiamazole* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *acetonitrile* and 95 volumes of *water*.

Mobile phase B 20 volumes of *acetonitrile* and 80 volumes of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4.5	100	0	isocratic
4.5-4.6	100→0	0→100	linear gradient
4.6-30	0	100	isocratic
30-30.1	0→100	100→0	linear gradient
30.1-40	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to carbimazole and thiamazole is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to thiamazole is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (2.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the test protected from light and prepare the solutions immediately before use.

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 20 mg of Carbimazole in 10 mL of *acetonitrile* with the aid of ultrasound for 5 minutes, filter through a nylon syringe filter and dilute 1 volume of this solution to 40 volumes with a 5% v/v solution of *acetonitrile*.
(2) 0.005% w/v of *carbimazole BPCRS* in mobile phase A.
(3) 0.01% w/v of *carbimazole BPCRS* and 0.0005% w/v of *thiamazole* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to carbimazole and thiamazole is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_{10}N_2O_2S$ in the tablets using the declared content of $C_7H_{10}N_2O_2S$ in *carbimazole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Carbimazole.

© Crown Copyright 2022

www.webofpharma.com

https://thuvienthuocngocanh.com/

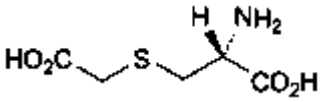
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Carbocisteine

General Notices

(Ph. Eur. monograph 0885)



$C_5H_9NO_4S$ 179.2 *638-23-3*

Action and use

Mucolytic.

Ph Eur

DEFINITION

Carbocisteine contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (2*R*)-2-amino-3-[(carboxymethyl)sulfanyl]propanoic acid, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *carbocisteine CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for ninhydrin-positive substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://nhathuocngocanh.com/

D. Dissolve 0.1 g in 4.5 mL of *dilute sodium hydroxide solution R*. Heat on a water-bath for 10 min. Cool and add 1 mL of a 25 g/L solution of *sodium nitroprusside R*. A dark red colour is produced, which changes to brown and then to yellow within a few minutes.

TESTS

Solution S

Disperse 5.00 g in 20 mL of *water R* and add dropwise with shaking 2.5 mL of *strong sodium hydroxide solution R*. Adjust to pH 6.3 with *1 M sodium hydroxide* and dilute to 50.0 mL with *water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

Shake 0.2 g with 20 mL of *carbon dioxide-free water R*. The pH of the suspension is 2.8 to 3.0.

Specific optical rotation (*2.2.7*)

-32.5 to -35.5, determined on solution S and calculated with reference to the dried substance.

Ninhydrin-positive substances

Examine by thin-layer chromatography (*2.2.27*), using a suitable silica gel as the coating substance.

Test solution (a) Dissolve 0.10 g of the substance to be examined in *dilute ammonia R2* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 50 mL with *water R*.

Reference solution (a) Dissolve 10 mg of *carbocisteine CRS* in *dilute ammonia R2* and dilute to 50 mL with the same solvent.

Reference solution (b) Dilute 5 mL of test solution (b) to 20 mL with *water R*.

Reference solution (c) Dissolve 10 mg of *carbocisteine CRS* and 10 mg of *arginine hydrochloride CRS* in 5 mL of *dilute ammonia R2* and dilute to 25 mL with *water R*.

Apply separately to the plate 5 µL of each solution. Allow the plate to dry in air. Develop over a path of 15 cm using a mixture of 20 volumes of *glacial acetic acid R*, 20 volumes of *water R* and 60 volumes of *butanol R*. Dry the plate in a current of warm air. Spray with *ninhydrin solution R* and heat at 100 °C to 105 °C for 15 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated principal spots.

Chlorides (*2.4.4*)

Dissolve 33 mg in 5 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*. The solution, without further addition of nitric acid, complies with the limit test for chlorides (0.15 per cent).

www.webofpharma.com

https://thuvienthuocngocanh.com/

Sulfates (*2.4.13*)

Dissolve 0.5 g in 5 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*. The solution complies with the limit test for sulfates (300 ppm).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Not more than 0.3 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 10 mL of *anhydrous formic acid R* with slight heating and shake until dissolution is complete. Add 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 17.92 mg of $C_5H_9NO_4S$.

STORAGE

Store protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thatuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbomer Eye Drops

General Notices

Action and use

Stabilizer in pharmaceutical products.

DEFINITION

Carbomer Eye Drops are a sterile viscous solution of Carbomer 940 or Carbomer 980 in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

IDENTIFICATION

A. Add 15 g of the eye drops to 85 mL of *water* and mix thoroughly. To 3 mL add 1 mL of *calcium chloride solution*, a fine white precipitate is produced.

B. Add 0.5 mL of *thymol blue solution* to 10 g of the eye drops. A yellow colour is produced. Add 0.5 mL of *cresol red solution* to 10 g of the eye drops. A yellow colour is produced.

TESTS

Acidity or alkalinity

pH, 6.6 to 7.1, Appendix V L.

Apparent viscosity

75 to 125% of the declared value when determined by the following method. Empty the contents of sufficient containers to obtain 200 g of the eye drops, taking care to avoid incorporation of air bubbles, and homogenise. Allow to stand at 25° for 60 minutes. Immerse the appropriate spindle of a rotational viscometer, switch on after 5 minutes and determine the *viscosity* at 25°, Appendix V H, Method III, using a shear speed of 5 per second.

Clarity of solution

The eye drops are not more opalescent than *reference suspension III*, Appendix IV A.

LABELLING

The label states the nominal viscosity in millipascal seconds.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Carbomers

General Notices

(Ph. Eur. monograph 1299)

Action and use

Stabilizer in pharmaceutical products.

Preparation

Carbomer Eye Drops

Ph Eur

DEFINITION

High-molecular-mass polymers of acrylic acid cross-linked with alkenyl ethers of sugars or polyalcohols.

Content

56.0 per cent to 68.0 per cent of carboxylic acid ($-CO_2H$) groups (dried substance).

CHARACTERS

Appearance

White or almost white, fluffy, hygroscopic powder.

Solubility

Swells in water and in other polar solvents after dispersion and neutralisation with sodium hydroxide solution.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Main bands At 1710 ± 5 cm^{-1}, 1454 ± 5 cm^{-1}, 1414 ± 5 cm^{-1}, 1245 ± 5 cm^{-1}, 1172 ± 5 cm^{-1}, 1115 ± 5 cm^{-1} and 801 ± 5 cm^{-1}, with the strongest band at 1710 ± 5 cm^{-1}.

B. Adjust a 10 g/L dispersion to about pH 7.5 with *1 M sodium hydroxide*. A highly viscous gel is formed.

C. Add 2 mL of a 100 g/L solution of *calcium chloride R*, with continuous stirring, to 10 mL of the gel from identification test B. A white precipitate is immediately produced.

D. Add 0.5 mL of *thymol blue solution R* to 10 mL of a 10 g/L dispersion. An orange colour is produced. Add 0.5 mL of *cresol red solution R* to 10 mL of a 10 g/L dispersion. A yellow colour is produced.

TESTS

Free acrylic acid

Liquid chromatography (*2.2.29*).

Test solution Mix 0.125 g of the substance to be examined with a 25 g/L solution of *aluminium potassium sulfate R* and dilute to 25.0 mL with the same solution. Heat the suspension at 50 °C for 20 min with shaking, then shake the suspension at room temperature for 60 min. Centrifuge and use the clear supernatant as the test solution.

Reference solution Dissolve 62.5 mg of *acrylic acid R* in a 25 g/L solution of *aluminium potassium sulfate R* and dilute to 100.0 mL with the same solution. Dilute 1.0 mL of this solution to 50.0 mL with a 25 g/L solution of *aluminium potassium sulfate R*.

Column:

— *size*: *l* = 0.12 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.361 g/L solution of *potassium dihydrogen phosphate R*, adjusted to pH 2.5 using *dilute phosphoric acid R*;

— *mobile phase B*: mixture of equal volumes of a 1.361 g/L solution of *potassium dihydrogen phosphate R* and *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	100	0
8 - 9	100 → 0	0 → 100
9 - 20	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 205 nm.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Injection 20 µL.

Retention time Acrylic acid = about 6.0 min.

Limit:

— *acrylic acid*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.25 per cent).

Benzene

Gas chromatography (*2.4.24, System A*).

Solution A Dissolve 0.100 g of *benzene R* in *dimethyl sulfoxide R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Test solution Weigh 50.0 mg of the substance to be examined into an injection vial and add 5.0 mL of *water R* and 1.0 mL of *dimethyl sulfoxide R*.

Reference solution Weigh 50.0 mg of the substance to be examined into an injection vial and add 4.0 mL of *water R*, 1.0 mL of *dimethyl sulfoxide R* and 1.0 mL of solution A.

Close the vials with a tight rubber membrane stopper coated with polytetrafluoroethylene and secure with an aluminium crimp cap. Shake to obtain a homogeneous dispersion.

Static head-space conditions that may be used:

— *equilibration temperature*: 80 °C;

— *equilibration time*: 60 min;

— *transfer-line temperature*: 90 °C.

Injection 1 mL of the gaseous phase of the test solution and 1 mL of the gaseous phase of the reference solution; repeat these injections twice more.

System suitability:

— *repeatability*: maximum relative standard deviation of the differences in area between the analyte peaks obtained from the 3 replicate pair injections of the reference solution and the test solution is 15 per cent.

Limit:

— *benzene*: the mean area of the peak due to benzene in the chromatograms obtained with the test solution is not greater than 0.5 times the mean area of the peak due to benzene in the chromatograms obtained with the reference solution (2 ppm).

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 60 min.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 4.0 per cent, determined on 1.0 g.

ASSAY

Slowly add 50 mL of *water R* to 0.120 g whilst stirring and heating at 60 °C for 15 min. Stop heating, add 150 mL of *water R* and continue stirring for 30 min. Add 2 g of *potassium chloride R* and titrate with *0.2 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.2 M sodium hydroxide* is equivalent to 9.0 mg of carboxylic acid ($-CO_2H$) groups.

STORAGE

In an airtight container.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for carbomers used as viscosity-increasing agents and gelling agents.

Apparent viscosity (*2.2.10*)

The nominal apparent viscosity is typically between 300 mPa·s and 115 000 mPa·s. For a product with a nominal apparent viscosity of 20 000 mPa·s or greater, the apparent viscosity is typically 70.0 per cent to 130.0 per cent of the nominal value; for a product with a nominal apparent viscosity of less than 20 000 mPa·s, the apparent viscosity is typically 50.0 per cent to 150.0 per cent of the nominal value.

Dry the substance to be examined *in vacuo* at 80 °C for 1 h. Carefully add 2.50 g of the previously dried substance to be examined to 500 mL of *water R* in a 1000 mL beaker while stirring continuously at 1000 ± 50 r/min, with the stirrer shaft set at an angle of 60° to one side of the beaker. Add the previously dried substance over a period of 45-90 s, at a uniform rate, ensuring that loose agglomerates of powder are broken up, and continue stirring at 1000 ± 50 r/min for 15 min. Remove the stirrer and place the beaker containing the dispersion in a water-bath at 25 ± 1 °C for 30 min. Insert the stirrer to a depth necessary to ensure that air is not drawn into the dispersion and, while stirring at 300 ± 25 r/min, adjust to pH 7.3-7.8 by adding a 180 g/L solution of *sodium hydroxide R* below the surface. The total volume of the 180 g/L solution of *sodium hydroxide R* used is about 6.2 mL. Allow 2-3 min before the final pH determination. If the final pH exceeds 7.8, discard the preparation and prepare another using a smaller amount of sodium hydroxide. Return the neutralised preparation

www.webofpharma.com

https://thuocngocanh.com/

to the water-bath at 25 °C for 1 h, then perform the viscosity determination without delay to avoid slight viscosity changes that occur 75 min after neutralisation. Determine the viscosity using a rotating viscometer with a spindle rotating at 20 r/min, using a spindle suitable for the expected apparent viscosity.

Carboxylic acid groups

See Assay.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbon Dioxide

General Notices

(Ph. Eur. monograph 0375)

Carbon Dioxide should be kept in approved metal cylinders which are painted grey and carry a label stating 'Carbon Dioxide'. In addition, 'Carbon Dioxide' or the symbol 'CO2' should be stencilled in paint on the shoulder of the cylinder.

CO_2 44.01 *124-38-9*

Ph Eur

DEFINITION

Content

Minimum 99.5 per cent *V/V* of CO_2 in the gaseous phase.

This monograph applies to carbon dioxide for medicinal use.

CHARACTERS

Appearance

Colourless gas.

Solubility

At 20 °C and at a pressure of 101 kPa, 1 volume dissolves in about 1 volume of water.

PRODUCTION

Examine the gaseous phase.

If the test is performed on a cylinder of gas, keep the cylinder of the substance to be examined at room temperature for not less than 6 h before carrying out the tests. Keep the cylinder in the vertical position with the outlet valve uppermost.

Carbon monoxide

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas A mixture containing 5 ppm *V/V* of *carbon monoxide R* in *nitrogen R1*.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *material*: stainless steel,

— *size*: *l* = 2 m, Ø = 4 mm,

— *stationary phase*: an appropriate molecular sieve for chromatography (0.5 nm).

Carrier gas helium for chromatography R.

Flow rate 60 mL/min.

Temperature:

— *column*: 50 °C,

— *injection port and detector*: 130 °C.

Detection Flame ionisation with methaniser.

Injection Loop injector.

Adjust the injected volumes and the operating conditions so that the height of the peak due to carbon monoxide in the chromatogram obtained with the reference gas is at least 35 per cent of the full scale of the recorder.

Limit:

— carbon monoxide: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (5 ppm *V/V*).

Nitrogen monoxide and nitrogen dioxide

Maximum 2 ppm *V/V* in total, determined using a chemiluminescence analyser (2.5.26).

Gas to be examined The substance to be examined.

Reference gas (a) Carbon dioxide R1.

Reference gas (b) A mixture containing 2 ppm *V/V* of nitrogen monoxide R in carbon dioxide R1 or in nitrogen R1.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of nitrogen monoxide and nitrogen dioxide in the gas to be examined.

If nitrogen is used instead of carbon dioxide in reference gas (b), multiply the result obtained by the quenching correction factor in order to correct the quenching effect on the analyser response caused by the carbon dioxide matrix effect.

The quenching correction factor is determined by applying a known reference mixture of nitrogen monoxide in carbon dioxide and comparing the actual content with the content indicated by the analyser which has been calibrated with a NO/N_2 reference mixture.

www.webofpharma.com

https://thuocngocanh.com/

$$\text{Quenching correction factor} = \frac{\text{actual nitrogen monoxide content}}{\text{indicated nitrogen monoxide content}}$$

Total sulfur

Maximum 1 ppm *V/V*, determined using an ultraviolet fluorescence analyser after oxidation of the sulfur compounds by heating at 1000 °C (Figure 0375.-1).

The apparatus consists of the following:

— a system generating ultraviolet radiation with a wavelength of 210 nm, made up of an ultraviolet lamp, a collimator, and a selective filter; the beam is blocked periodically by a chopper rotating at high speed,

— a reaction chamber through which flows the previously filtered gas to be examined,

— a system that detects radiation emitted at a wavelength of 350 nm, made up of a selective filter, a photomultiplier tube and an amplifier.

Gas to be examined The substance to be examined.

Reference gas (a) *Carbon dioxide R1*.

Reference gas (b) A mixture containing between 0.5 ppm *V/V* and 2 ppm *V/V* of *hydrogen sulfide R1* in *carbon dioxide R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Pass the gas to be examined through a quartz oven heated to 1000 °C. *Oxygen R* is circulated in the oven at a tenth of the flow rate of the gas to be examined. Measure the sulfur dioxide content in the gaseous mixture leaving the oven.

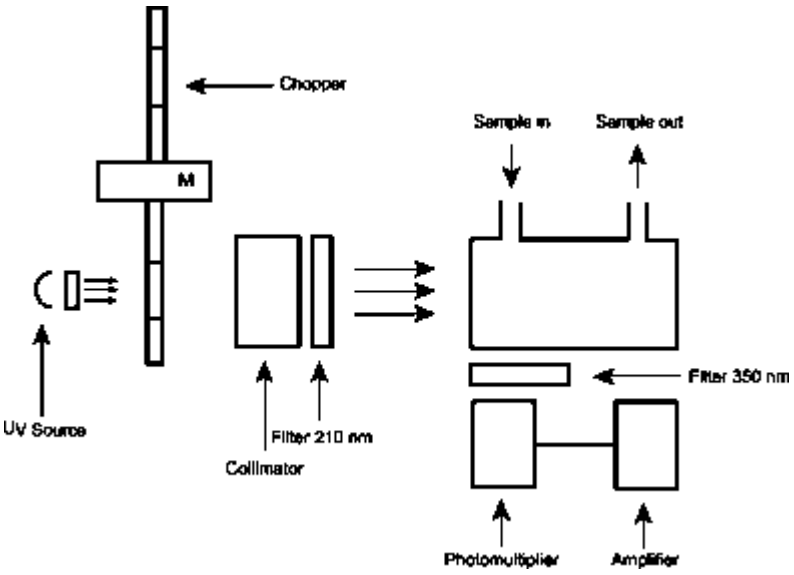


Figure 0375.-1.– *UV Fluorescence Analyser*

Water

Maximum 67 ppm *V/V*, determined using an electrolytic hygrometer (*2.5.28*).

www.webofpharma.com

https://thuocngocanh.com/

Assay

Infrared analyser (2.5.24).

Gas to be examined The substance to be examined. It must be filtered to avoid stray light phenomena.

Reference gas (a) Carbon dioxide R1.

Reference gas (b) A mixture containing 95.0 per cent *V/V* of carbon dioxide R1 and 5.0 per cent *V/V* of nitrogen R1.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon dioxide in the gas to be examined.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison Ph. Eur. reference spectrum of carbon dioxide.

B. Place a glowing splinter of wood in an atmosphere of the substance to be examined. It is extinguished.

C. Pass a stream of the substance to be examined through barium hydroxide solution R. A white precipitate is formed which dissolves with effervescence in dilute acetic acid R.

TESTS

Examine the gaseous phase.

If the test is performed on a cylinder of gas, keep the cylinder of the substance to be examined at room temperature for not less than 6 h before carrying out the tests. Keep the cylinder in the vertical position with the outlet valve uppermost.

Carbon monoxide

Maximum 5 ppm *V/V*, determined using a carbon monoxide detector tube (2.1.6).

Hydrogen sulfide

Maximum 1 ppm *V/V*, determined using a hydrogen sulfide detector tube (2.1.6).

Nitrogen monoxide and nitrogen dioxide

Maximum 2 ppm *V/V* in total, determined using a nitrogen monoxide and nitrogen dioxide detector tube (2.1.6).

Sulfur dioxide

Maximum 2 ppm *V/V*, determined using a sulfur dioxide detector tube (2.1.6).

www.webofpharma.com

https://thuathuocngocanh.com/

Water vapour

Maximum 67 ppm *V/V*, determined using a water vapour detector tube (2.1.6).

STORAGE

Store liquefied under pressure in suitable containers complying with the legal regulations.

IMPURITIES

A. NO: nitrogen monoxide,

B. NO_2: nitrogen dioxide,

C. CO: carbon monoxide,

D. total sulfur,

E. H_2O: water.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbon Monoxide

General Notices

(Ph. Eur. monograph 2408)

CO 28.00 *630-08-0*

Ph Eur

DEFINITION

Gas obtained by steam reforming (catalytic oxidation) of hydrocarbons.

Content

Minimum 99.5 per cent *V/V* of CO.

This monograph applies to carbon monoxide for medicinal use.

CHARACTERS

Appearance

Colourless, flammable gas.

Solubility

At 20 °C and at a pressure of 101 kPa, 2.266 volumes of carbon monoxide dissolve in 100 volumes of water.

IDENTIFICATION

Carry out either test A or B.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of carbon monoxide*.

B. It complies with the limits of the assay.

TESTS

Carbon dioxide

Gas chromatography (*2.2.28*).

www.webofpharma.com

https://thuocngocanh.com/

Gas to be examined The substance to be examined.

Reference gas A mixture containing 300 ppm *V/V* of *carbon dioxide R1* in *carbon monoxide R*.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: an appropriate divinylbenzene porous polymer (149-177 µm).

Carrier gas *helium for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 50 °C;

— *detector*: 220 °C.

Detection Thermal conductivity.

Injection 1 mL.

Run time 3 min.

Relative retention With reference to carbon monoxide (retention time = about 0.4 min): carbon dioxide = about 3.5.

Limit:

— *carbon dioxide*: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (300 ppm *V/V*).

Methane

Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas A mixture containing 100 ppm *V/V* of *methane R* in *carbon monoxide R*.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 4 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (177-250 µm).

www.webofpharma.com

https://thuvienthuocngocanh.com/

Carrier gas *nitrogen for chromatography R*.

Flow rate 10 mL/min.

Temperature:

— *column*: 95 °C;

— *detector*: 240 °C.

Detection Flame ionisation.

Injection 1 mL.

Run time 3 min.

Retention time Methane = about 1.8 min.

Limit:

— *methane*: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (100 ppm *V/V*).

Hydrogen

Gas chromatography.

Gas to be examined The substance to be examined.

Reference gas A mixture containing 300 ppm *V/V* of *hydrogen for chromatography R* in *carbon monoxide R*.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: molecular sieve for chromatography (149-177 µm) with a nominal pore size of 0.5 nm.

Carrier gas *argon for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 100 °C;

— *detector*: 160 °C.

Detection Thermal conductivity.

Injection 1 mL.

www.webofpharma.com

https://thuocngocanh.com/

Run time 4 min.

Relative retention With reference to carbon monoxide (retention time = about 2.3 min): hydrogen = about 0.4.

Limit:

— *hydrogen*: not more than the area of the corresponding peak in the chromatogram obtained with the reference gas (300 ppm *V/V*).

Nickel tetracarbonyl and iron pentacarbonyl

Not detectable, using a detector tube having a limit of detection of 0.1 ppm *V/V* (*2.1.6*).

Water

Maximum 10 ppm *V/V*, determined using an electrolytic hygrometer (*2.5.28*).

ASSAY

Infrared analyser (*2.5.25*).

Gas to be examined The substance to be examined, previously filtered to avoid stray light phenomena.

Reference gas (a) *Carbon monoxide R*.

Reference gas (b) A mixture containing 95.0 per cent *V/V* of *carbon monoxide R* and 5.0 per cent *V/V* of *nitrogen R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon monoxide in the gas to be examined.

STORAGE

Under pressure in suitable containers complying with the legal regulations.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*

A. CO_2: carbon dioxide,

B. CH_4: methane,

C. H_2: hydrogen,

D. $Ni(CO)_4$: nickel tetracarbonyl,

E. $Fe(CO)_5$: iron pentacarbonyl,

F. H_2O: water.

Ph Eur

www.webofpharma.com

https://thuvienthuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carbon Monoxide Intermix (5 per cent) in Nitrogen

General Notices

(Ph. Eur. monograph 2904)

Ph Eur

DEFINITION

A mixture containing 5 per cent *V/V* of *Carbon monoxide (2408)* in *Low-oxygen nitrogen (1685)*.

Content

4.75 per cent *V/V* to 5.25 per cent *V/V* of carbon monoxide (CO) in nitrogen (N_2).

This monograph applies to carbon monoxide intermix (5 per cent) in nitrogen used in the preparation of lung function test gas mixtures for medicinal use.

CHARACTERS

Appearance

Colourless gas.

IDENTIFICATION

Carry out either tests A, C or tests B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of carbon monoxide*.

B. It complies with the limits of the assay.

C. Gas chromatography (*2.2.28*).

Gas to be examined The substance to be examined.

Reference gas *Nitrogen R1*.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

www.webofpharma.com

https://thuathuocngocanh.com/

— *stationary phase*: *molecular sieve for chromatography R* (0.5 nm).

Carrier gas *helium for chromatography R*.

Flow rate 20 mL/min.

Temperature:

— *column*: 80 °C;

— *detector*: 130 °C.

Detection Thermal conductivity.

Injection 10 µL.

Retention time Nitrogen = about 2 min.

Results The principal peak in the chromatogram obtained with the gas to be examined is similar in retention time to the principal peak in the chromatogram obtained with the reference gas.

TESTS

Water (*2.5.28*)

Maximum 10 ppm *V/V*.

ASSAY

Infrared analyser (*2.5.25*).

Gas to be examined The substance to be examined. It must be filtered to avoid stray-light phenomena.

Reference gas (a) Mixture containing 5.0 per cent *V/V* of *carbon monoxide R* in *nitrogen R1*.

Reference gas (b) *Nitrogen R1*.

Calibrate the apparatus and set the sensitivity using reference gases (a) and (b). Measure the content of carbon monoxide in the gas to be examined.

STORAGE

As a compressed gas, in appropriate high-pressure cylinders complying with the legal regulations.

LABELLING

The label states the nominal content, in per cent *V/V*, of carbon monoxide in nitrogen.

www.webofpharma.com

https://thuathuocngocanh.com/

IMPURITIES

Specified impurities A.

A. water.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

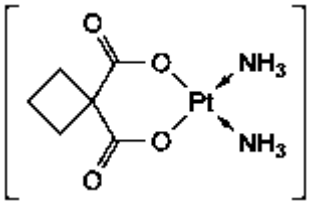
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carboplatin

General Notices

(Ph. Eur. monograph 1081)



$C_6H_{12}N_2O_4Pt$ 371.3 *41575-94-4*

Action and use

Platinum-containing cytotoxic.

Preparation

Carboplatin Injection

Ph Eur

DEFINITION

(*SP*-4-2)-Diammine[cyclobutan-1,1-di(carboxylato-κ*O*)(2-)]platinum.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Colourless, crystalline powder.

Solubility

Sparingly soluble in water, very slightly soluble in acetone and in ethanol (96 per cent).

mp

About 200 °C, with decomposition.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of carboplatin*.

TESTS

Solution S

Dissolve 0.25 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Impurity B and acidity

Maximum 0.5 per cent, calculated as impurity B.

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.7 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in a mixture of equal volumes of *acetonitrile R* and *water R* and dilute to 20.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *cisplatin CRS* (impurity A) in the mobile phase and dilute to 5.0 mL with the mobile phase. Dilute 0.5 mL of the solution to 200.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *acetonitrile for chromatography R* (13:87 *V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Run time 2.5 times the retention time of carboplatin.

Relative retention With reference to carboplatin (retention time = about 7 min): impurity A = about 0.3.

System suitability Test solution:

— *number of theoretical plates*: minimum 5000; if necessary, adjust the concentration of acetonitrile in the mobile phase;

— *symmetry factor*: maximum 2.0; if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dissolve 0.5 g in *water R*, heating slightly if necessary, and dilute to 20 mL with the same solvent. Filter if necessary. Dilute 10 mL of this solution to 15 mL with *water R*. Prepare the standard using 5 mL of *chloride standard solution (5 ppm Cl) R*.

Ammonium (*2.4.1, Method B*)

Maximum 100 ppm, determined on 0.20 g.

Prepare the standard using 0.2 mL of *ammonium standard solution (100 ppm NH_4) R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Use the residue obtained in the test for loss on drying. Ignite 0.200 g of the residue to constant mass at 800 ± 50 °C.

1 mg of the residue is equivalent to 1.903 mg of $C_6H_{12}N_2O_4Pt$.

STORAGE

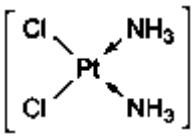
Protected from light.

IMPURITIES

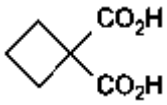
www.webofpharma.com

https://thuathuocngocanh.com/

Specified impurities *A, B.*



A. (*SP*-4-2)-diamminedichloridoplatinum(II) (cisplatin),



B. cyclobutane-1,1-dicarboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carboplatin Injection

General Notices

Action and use

Platinum-containing cytotoxic.

DEFINITION

Carboplatin Injection is a sterile solution of Carboplatin in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of carboplatin, $C_6H_{12}N_2O_4Pt$

90.0 to 105.0% of the stated amount.

Carry out the following procedures protected from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions within 2 hours of preparation.

(1) Use the injection diluted, if necessary, with *water* to produce a solution containing 0.1% w/v of Carboplatin.

(2) 0.1% w/v of *carboplatin BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air for 2 hours. Spray the plate with a solution prepared immediately before use by dissolving 5.6 g of *tin(II)chloride* in 10 mL of *hydrochloric acid* (dissolution may not be complete, filter if necessary), adding 90 mL of *water* and 1 g of *potassium iodide* and stirring. Heat the plate at 100° for 10 minutes and examine in daylight.

MOBILE PHASE

20 volumes of *water* and 80 volumes of *acetone*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acidity

pH, 5.0 to 7.0, Appendix V L.

Cyclobutane-1,1-dicarboxylic acid

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection with *water* to produce a solution containing 0.1% w/v of Carboplatin; use within 2 hours of preparation.

(2) 0.001% w/v of *cyclobutane-1,1-dicarboxylic acid* in *water*.

(3) Mix 1 volume of solution (1) with 1 volume of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless-steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µ-Bondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 100 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 2.5 times the retention time of the principal peak.

MOBILE PHASE

20 volumes of solution A prepared as described below, 100 volumes of *acetonitrile* and 880 volumes of *water*. To prepare solution A dissolve 8.5 g of *tetrabutylammonium hydrogen sulfate* in 80 mL of *water*, add 3.4 mL of *orthophosphoric acid* and adjust the pH to 7.55 with 10M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peak due to carboplatin and that due to cyclobutane-1,1-dicarboxylic acid is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to cyclobutane-1,1-dicarboxylic acid is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection with *water BET*, if necessary, to contain 10 mg of Carboplatin per mL (solution A). The endotoxin limit concentration of solution A is 5.4 IU of endotoxin per mL.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions within 2 hours of preparation.

(1) Dilute the injection with *water* to produce a solution containing 0.1% w/v of Carboplatin.

(2) 0.1% w/v of *carboplatin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless-steel column (30 cm × 3.9 mm) packed with *aminopropylsilyl silica gel for chromatography* (10 µm) (µ-Bondapak-NH_2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

130 volumes of *water* and 870 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (1), the *capacity factor* is not less than 4.0, the number of *theoretical plates* is not less than 5000 and the *symmetry factor* is not more than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_6H_{12}N_2O_4Pt$ in the injection using the declared content of $C_6H_{12}N_2O_4Pt$ in *carboplatin BPCRS*.

STORAGE

Carboplatin Injection should be protected from light and free from contact with metals.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Carboplatin.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

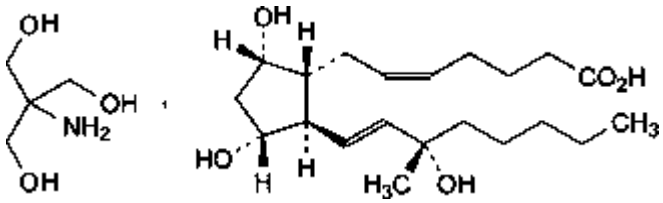
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carboprost Trometamol

General Notices

(Ph. Eur. monograph 1712)



$C_{25}H_{47}NO_8$ 489.7 *58551-69-2*

Action and use

Prostaglandin ($PGF_{2\alpha}$) analogue.

Ph Eur

DEFINITION

2-Amino-2-(hydroxymethyl)propane-1,3-diol (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-3-methyloct-1-enyl]cyclopentyl]hept-5-enoate ((15*S*)-15-methyl-PGF_2).

Content

94.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Soluble in water.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://nhathuocngocanh.com/

Comparison *Ph. Eur. reference spectrum of carboprost trometamol*.

TESTS

Specific optical rotation (*2.2.7*)

+ 18 to + 24 (anhydrous substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 15.0 mg of the substance to be examined in a mixture of 23 volumes of *acetonitrile R* and 77 volumes of *water for chromatography R* and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 15.0 mg of *carboprost trometamol CRS* (containing impurity A) in a mixture of 23 volumes of *acetonitrile R* and 77 volumes of *water for chromatography R* and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (b) Dilute 1.0 mL of reference solution (a) and 0.15 mL of *(15R)-15-methylprostaglandin $F_{2\alpha}$ R* (impurity B) to 100.0 mL with a mixture of 23 volumes of *acetonitrile R* and 77 volumes of *water for chromatography R*.

Reference solution (c) Dilute 2.0 mL of the test solution to 20.0 mL with a mixture of 23 volumes of *acetonitrile R* and 77 volumes of *water for chromatography R*. Dilute 2.0 mL of this solution to 20.0 mL with a mixture of 23 volumes of *acetonitrile R* and 77 volumes of *water for chromatography R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm) with a pore size of 8-10 nm and a carbon loading of 12-19 per cent.

Mobile phase Mix 23 volumes of *acetonitrile R1* and 77 volumes of a 2.44 g/L solution of *sodium dihydrogen phosphate R* in *water for chromatography R* previously adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 20 µL.

Run time 1.3 times the retention time of carboprost.

Relative retention With reference to carboprost (retention time = about 80 min): impurity B = about 0.85; impurity A = about 0.9.

Identification of impurities Use the chromatogram obtained with reference solution (a) and the chromatogram supplied with *carboprost trometamol CRS* to identify the peak due to impurity A.

www.webofpharma.com

https://thuocngocanh.com/

System suitability:

— *resolution*: minimum 3.4 between the peaks due to impurity B and carboprost in the chromatogram obtained with reference solution (b);

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B in the chromatogram obtained with reference solution (a).

Limits:

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 per cent),

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent),

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent),

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (4.0 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 50 mg.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mix 27 volumes of *acetonitrile R1* and 73 volumes of a 2.44 g/L solution of *sodium dihydrogen phosphate R* in *water for chromatography R* previously adjusted to pH 2.5 with *phosphoric acid R*.

Injection Test solution and reference solution (a).

Run time 1.2 times the retention time of carboprost.

Retention time Carboprost = about 29 min.

Calculate the percentage content of $C_{25}H_{47}NO_8$ using the declared content of *carboprost trometamol CRS*.

STORAGE

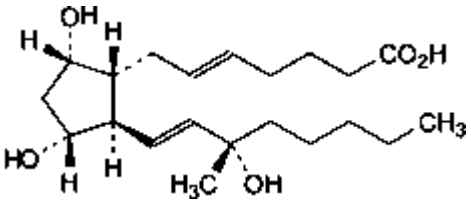
At a temperature below -15 ° C.

IMPURITIES

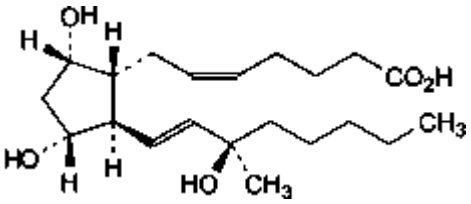
www.webofpharma.com

https://thuocngocanh.com/

Specified impurities *A, B.*



A. (5*E*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-3-methyloct-1-enyl]cyclopentyl]hept-5-enoic acid,



B. (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-3-methyloct-1-enyl]cyclopentyl]hept-5-enoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carmellose[1]

General Notices

(Ph. Eur. monograph 2360)

9000-11-7

Action and use

Excipient; bulk laxative.

Ph Eur

DEFINITION

Carboxymethylether of cellulose.

Partly *O*-carboxymethylated cellulose.

♦ CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Practically insoluble in anhydrous ethanol. It swells with water to form a suspension and becomes viscid in 1 M sodium hydroxide.♦

IDENTIFICATION

A. pH (*2.2.3*): 3.5 to 5.0.

Suspend 1.0 g in 100 mL of *carbon dioxide-free water R*.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *carmellose CRS*.

TESTS

Chlorides

Maximum 0.36 per cent.

www.webofpharma.com

https://thuathuocngocanh.com/

Shake 0.8 g with 50 mL of *water R*, dissolve in 10 mL of *1 M sodium hydroxide* and dilute to 100 mL with *water R*. Heat on a water-bath a mixture of 10 mL of *dilute nitric acid R* and 20 mL of this solution until a flocculent precipitate is produced. Cool, centrifuge and take out the supernatant. Wash the precipitate with 3 quantities, each of 10 mL, of *water R*, centrifuging each time. Combine the supernatant and the washings and dilute to 100 mL with *water R*. To 25 mL of this solution add 6 mL of *dilute nitric acid R* and dilute to 50 mL with *water R* (test solution). Prepare the reference solution in the same manner, using 0.40 mL of *0.01 M hydrochloric acid*. Add 1 mL of *silver nitrate solution R2* to the test solution and the reference solution. Allow to stand protected from light for 5 min. Any opalescence in the test solution is not more intense than that in the reference solution.

Sulfates

Maximum 0.72 per cent.

Shake 0.40 g with 25 mL of *water R*, dissolve in 5 mL of *1 M sodium hydroxide* and add 20 mL of *water R*. Heat this solution with 2.5 mL of *hydrochloric acid R* in a water-bath until a flocculent precipitate is produced. Cool, centrifuge, and take out the supernatant. Wash the precipitate with 3 quantities, each of 10 mL, of *water R*, centrifuging each time. Combine the supernatant and the washings, and dilute to 100 mL with *water R*. Filter, and discard the first 5 mL of the filtrate. To 25 mL of the filtrate add 1 mL of *dilute hydrochloric acid R* and dilute to 50 mL with *water R* (test solution). Prepare the reference solution in the same manner, using 1.5 mL of *0.005 M sulfuric acid*. Add 2 mL of a 120 g/L solution of *barium chloride R* to the test solution and the reference solution. Mix and allow to stand for 10 min. The white turbidity produced in the test solution is not thicker than that in the reference solution.

Loss on drying (*2.2.32*)

Maximum 8.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 1.5 per cent (dried substance), determined on 1.0 g.

♦ STORAGE

In an airtight container.♦

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carmellose Calcium[1]

General Notices

(Ph. Eur. monograph 0886)

9050-04-8

Action and use

Excipient in pharmaceutical products; bulk laxative.

Ph Eur

DEFINITION

Calcium salt of partly *O*-carboxymethylated cellulose. Calcium salt of a polycarboxymethyl ether of cellulose.

♦ CHARACTERS

Appearance

White or yellowish-white powder, hygroscopic after drying.

Solubility

Practically insoluble in acetone, in ethanol (96 per cent) and in toluene. It swells with water to form a suspension.♦

IDENTIFICATION

A. Shake 0.1 g thoroughly with 10 mL of *water R*. Add 2 mL of a 42 g/L solution of *sodium hydroxide R* and allow to stand for 10 min (solution A). Dilute 1 mL of solution A to 5 mL with *water R*. To 0.05 mL of this solution add 0.5 mL of a 0.5 g/L solution of *chromotropic acid, sodium salt R* in a 75 per cent *m/m* solution of *sulfuric acid R* and heat on a water-bath for 10 min. A reddish-violet colour develops.

B. Shake 5 mL of solution A obtained in identification test A with 10 mL of *acetone R*. A white, flocculent precipitate is produced.

C. Shake 5 mL of solution A obtained in identification test A with 1 mL of *ferric chloride solution R1*. A brown, flocculent precipitate is formed.

D. Ignite 1 g to ash and dissolve the residue in a mixture of 5 mL of *acetic acid R* and 10 mL of *water R*. Filter if necessary and heat the filtrate to boiling. Cool and neutralise with *dilute ammonia R1*. The solution gives reaction (a) of calcium (*2.3.1*).

TESTS

Solution S

Shake 1.0 g with 50 mL of *distilled water R*, add 5 mL of *dilute sodium hydroxide solution R* and dilute to 100 mL with *distilled water R*.

www.webofpharma.com

https://thuocngocanh.com/

Alkalinity

Shake 1.0 g thoroughly with 50 mL of *carbon dioxide-free water R* and add 0.1 mL of *phenolphthalein solution R*. No red colour develops.

Chlorides (*2.4.4*)

Maximum 0.36 per cent.

Heat 28 mL of solution S with 10 mL of *dilute nitric acid R* on a water-bath until a flocculent precipitate is produced. Cool, centrifuge and separate the supernatant. Wash the precipitate with 3 quantities, each of 10 mL, of *water R*, centrifuging each time. Combine the supernatant and the washings and dilute to 100 mL with *water R*. To 25 mL add 6 mL of *dilute nitric acid R* and dilute to 50 mL with *water R*. Dilute 10 mL of the solution to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 1 per cent.

Heat 20 mL of solution S with 1 mL of *hydrochloric acid R* on a water-bath until a flocculent precipitate is produced. Cool, centrifuge and separate the supernatant. Wash the precipitate with 3 quantities, each of 10 mL, of *distilled water R*, centrifuging each time. Combine the supernatant and the washings and dilute to 100 mL with *distilled water R*. To 25 mL add 1 mL of *dilute hydrochloric acid R* and dilute to 50 mL with *distilled water R*.

Loss on drying (*2.2.32*)

Maximum 10.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

10.0 per cent to 20.0 per cent, determined on 1.0 g of the dried substance.

♦ STORAGE

In an airtight container.♦

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carmellose Sodium

General Notices

(Ph. Eur. monograph 0472)

9004-32-4

Action and use

Excipient; bulk laxative.

Preparation

Carmellose Sodium Eye Drops

Ph Eur

DEFINITION

Carboxymethylcellulose sodium. Sodium salt of a partly *O*-carboxymethylated cellulose.

Content

6.5 per cent to 10.8 per cent of sodium (Na) (dried substance).

CHARACTERS

Appearance

White or almost white, granular powder, hygroscopic after drying.

Solubility

Practically insoluble in acetone, in anhydrous ethanol and in toluene. It is easily dispersed in water giving colloidal solutions.

IDENTIFICATION

A. To 10 mL of solution S (see Tests) add 1 mL of *copper sulfate solution R*. A blue, cotton-like precipitate is formed.

B. Boil 5 mL of solution S for a few minutes. No precipitate is formed.

C. To the residue obtained in the determination of the sulfated ash, add 1 mL of *hydrochloric acid R* and evaporate on a water-bath. Take up the residue in 20 mL of *water R*. The solution gives the reactions of sodium (2.3.1).

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Sprinkle a quantity of the substance to be examined equivalent to 1.0 g of the dried substance onto 90 mL of *carbon dioxide-free water R* at 40 °C to 50 °C stirring vigorously. Continue stirring until a colloidal solution is obtained, cool and dilute to 100 mL with *carbon dioxide-free water R*.

Appearance of solution

Solution S is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 6.0 to 8.0.

Viscosity

75 per cent to 140 per cent of the value stated on the label.

While stirring, introduce a quantity of the substance to be examined equivalent to 2.00 g of the dried substance into 50 mL of *water R* heated to 90 °C. For a product of low viscosity, use, if necessary, the quantity required to give the concentration indicated on the label. Allow to cool, dilute to 100.0 mL with *water R* and stir until dissolution is complete. Determine the viscosity (*2.2.10*) using a rotating viscometer at 20 °C and a shear rate of 10 s^{-1}. If it is impossible to obtain a shear rate of exactly 10 s^{-1}, use a shear rate slightly higher and a rate slightly lower and interpolate.

Sodium glycolate

Maximum 0.4 per cent (dried substance).

Test solution Place a quantity of the substance to be examined equivalent to 0.500 g of dried substance in a beaker. Add 5 mL of *acetic acid R* and 5 mL of *water R*. Stir until dissolution is complete (about 30 min). Add 80 mL of *acetone R* and 2 g of *sodium chloride R*. Filter through a fast filter paper impregnated with *acetone R* into a volumetric flask, rinse the beaker and filter with *acetone R* and dilute the filtrate to 100.0 mL with the same solvent. Allow to stand for 24 h without shaking. Use the clear supernatant.

Reference solution In a volumetric flask, dissolve 0.310 g of *glycolic acid R*, previously dried in a desiccator (*2.2.32*), in *water R* and dilute to 1000.0 mL with the same solvent. Place 5.0 mL of this solution in a volumetric flask, add 5 mL of *acetic acid R* and allow to stand for about 30 min. Add 80 mL of *acetone R* and 2 g of *sodium chloride R* and dilute to 100.0 mL with *acetone R*.

Place 2.0 mL of each solution in a separate 25 mL volumetric flask. Heat on a water-bath to eliminate acetone. Cool to room temperature and add 5.0 mL of *2,7-dihydroxynaphthalene solution R* to each flask. Shake and add 15.0 mL of *2,7-dihydroxynaphthalene solution R*. Close the flasks with aluminium foil and heat on a water-bath for 20 min. Cool under running water and dilute to 25.0 mL with *sulfuric acid R*. Within 10 min, transfer 10.0 mL of each solution to a flat-bottomed tube. Examine the solutions viewing vertically. The test solution is not more intensely coloured than the reference solution.

Chlorides (*2.4.4*)

Maximum 0.25 per cent.

www.webofpharma.com

https://thuathuocngocanh.com/

Dilute 2 mL of solution S to 15 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 10.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

20.0 per cent to 33.3 per cent, determined on 1.0 g using a mixture of equal volumes of *sulfuric acid R* and *water R* and calculated with reference to the dried substance. These limits correspond to a content of 6.5 per cent to 10.8 per cent of sodium (Na).

LABELLING

The label states:

— the viscosity in millipascal seconds for a 20 g/L solution;

— for a product of low viscosity, the concentration of the solution to be used and the viscosity in millipascal seconds.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carmellose Sodium Eye Drops

General Notices

Action and use

Used in the treatment of tear deficiency.

DEFINITION

Carmellose Sodium Eye Drops are a sterile colloidal solution of Carmellose Sodium in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of carmellose sodium

95.0 to 115.0% of the stated amount.

IDENTIFICATION

A. To 10 mL of the eye drops, add 1 mL of *copper sulfate solution*. A blue, cotton-like precipitate is formed.

B. In the Assay, the spectrum obtained with solution (1) shows maxima at about 295, 366, 519 and 635 nm. The spectrum obtained with solution (1) corresponds to the spectrum obtained with solution (2).

TESTS

Clarity and colour of solution

The eye drops are *clear*, Appendix IV A, and are not more intensely coloured than *reference solution* Y_6, Appendix IV B, Method II.

Acidity or alkalinity

pH, 6.0 to 8.0, Appendix V L.

Osmolality

The osmolality of the eye drops is 270 to 350 mosmol/kg, Appendix V N.

ASSAY

Dissolve 3.75 g of *diphenylamine* in 150 mL of *glacial acetic acid*, add 90 mL of *hydrochloric acid* and mix well (solution A).

For solution (1), use the eye drops, diluted if necessary, with *water* to contain 0.01% w/v of Carmellose Sodium. Pipette 2 mL of this solution into a glass stoppered test tube, add 5 mL of solution A, mix and immediately immerse the test tube in an oil bath maintained at

www.webofpharma.com

https://thuocngocanh.com/

105° to 110° for 30 minutes, the bath temperature being kept uniform to within 0.1° during this time. Remove the test tube, place in an ice bath until cooled and allow to equilibrate to room temperature for not more than 1 hour. For solution (2), prepare a solution containing 0.01% w/v of *carmellose sodium BPCRS* in *water* and treat at the same time and in the same manner as solution (1), starting at the words “pipette 2 mL of this solution ….”. For solution (3), use *water* and treat at the same time and in the same manner as solution (1), starting at the words “pipette 2 mL of this solution….”.

Measure the *absorbance* of solution (1) and solution (2) at the maximum at about 635 nm, Appendix II B, using solution (3) in the reference cell. Calculate the content of Carmellose Sodium in the eye drops from the values of the absorbances obtained and using the declared content of Carmellose Sodium in *carmellose sodium BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

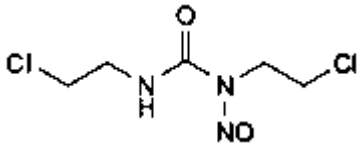
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carmustine

General Notices

(Ph. Eur. monograph 1187)



$C_5H_9Cl_2N_3O_2$ 214.1 *154-93-8*

Action and use

Cytotoxic alkylating agent.

Ph Eur

DEFINITION

N,*N*′-Bis(2-chloroethyl)-*N*-nitrosourea.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellowish, granular powder.

Solubility

Very slightly soluble in water, very soluble in methylene chloride, freely soluble in anhydrous ethanol.

mp

About 31 °C, with decomposition.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Preparation Examine the melted substance prepared as a film.

Comparison *carmustine CRS*.

TESTS

Impurity B

Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.20 g of the substance to be examined in 0.5 mL of *methanol R*.

Reference solution (a) Dissolve 30.0 mg of *chloroethylamine hydrochloride R* (impurity B) in 25 mL of *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dissolve 0.20 g of the substance to be examined in 0.5 mL of reference solution (a).

Plate *TLC silica gel plate R*.

Mobile phase:

— *mobile phase A*: *ethyl acetate R*;

— *mobile phase B*: *methanol R*, *ethyl acetate R* (30:70 *V/V*).

Application 1 µL.

Development Over 2/3 of the plate with mobile phase A, allow to dry in air for 5 min; over 1/3 of the plate with mobile phase B, allow to dry in air for 10 min.

Detection Spray with *diethylamine R* and heat at 105 °C for 20 min; allow to cool and spray with *silver nitrate solution R2*. Expose to ultraviolet light at 365 nm until brown to black spots appear and examine in daylight.

Retardation factors Impurity B = about 0.2; carmustine = about 0.9.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity B*: any spot due to impurity B is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.1 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light. Prepare the solutions immediately before use.*

Solvent mixture *ethanol (96 per cent) R*, *water R* (10:90 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 20.0 mg of the substance to be examined in 1 mL of *ethanol (96 per cent) R* and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *carmustine impurity A CRS* in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 25.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) To 1 mL of the test solution add 1 mL of reference solution (b) and dilute to 100 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 2.7 g of *potassium dihydrogen phosphate R* in 1000 mL of *water for chromatography R*, add 1 mL of *triethylamine R* and adjust to pH 3.5 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	85	15
10 - 60	85 → 30	15 → 70

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 230 nm and, for impurity A, at 205 nm.

Autosampler Set at 5 °C.

Injection 20 µL of the test solution and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to carmustine (retention time = about 36 min): impurity A = about 0.3.

System suitability Reference solution (d):

— *resolution*: minimum 5.0 between the peaks due to impurity A and carmustine.

www.webofpharma.com

https://thuocngocanh.com/

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (c);

— for impurities other than A, use the concentration of carmustine in reference solution (a).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

maximum 1.0 per cent, determined on 0.500 g.

ASSAY

Dissolve 0.100 g in 30 mL of *anhydrous ethanol R* and dilute to 100.0 mL with *water R*. Dilute 3.0 mL of the solution to 100.0 mL with *water R*. Measure the absorbance (2.2.25) at the absorption maximum at 230 nm.

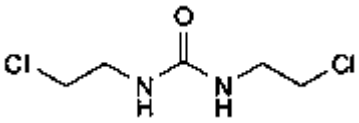
Calculate the content of $C_5H_9Cl_2N_3O_2$ taking the specific absorbance to be 270.

STORAGE

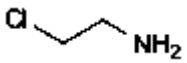
In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities A, B.



A. *N*,*N*′-bis(2-chloroethyl)urea,



B. 2-chloroethan-1-amine.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carnauba Wax

General Notices

(Ph. Eur. monograph 0597)

8015-86-9

Action and use

Excipient.

Ph Eur

DEFINITION

Purified wax obtained from the leaves of *Copernicia cerifera* Mart.

CHARACTERS

Appearance

Pale yellow or yellow powder, flakes or hard masses.

Solubility

Practically insoluble in water, soluble on heating in ethyl acetate and in xylene, practically insoluble in ethanol (96 per cent).

Relative density

About 0.97.

IDENTIFICATION

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined with heating in 5 mL of *chloroform R*. Use the warm solution.

Reference solution Dissolve 5 mg of *menthol R*, 5 µL of *menthyl acetate R* and 5 mg of *thymol R* in 10 mL of *toluene R*.

Plate *TLC silica gel plate R*.

Mobile phase *ethyl acetate R*, *chloroform R* (2:98 *V/V*).

Application 30 µL of the test solution and 10 µL of the reference solution as bands 20 mm by 3 mm.

www.webofpharma.com

https://thuocngocanh.com/

Development Over 1/2 of the plate.

Drying In air.

Detection Spray with a freshly prepared 200 g/L solution of *phosphomolybdic acid R* in *ethanol (96 per cent) R* (about 10 mL for a 20 cm plate). Heat at 100-105 °C for 10-15 min.

Results The chromatogram obtained with the reference solution shows in the lower part a dark blue zone (menthol), above this zone a reddish zone (thymol) and in the upper part a dark blue zone (menthyl acetate). The chromatogram obtained with the test solution shows a large blue zone (triacontanol = melissyl alcohol) at a level between the thymol and menthol zones in the chromatogram obtained with the reference solution. Further blue zones are visible in the upper part of the chromatogram obtained with the test solution, at levels between those of the menthyl acetate and thymol zones in the chromatogram obtained with the reference solution; above these zones, further zones are visible in the chromatogram obtained with the test solution; the zone with the highest R_F value is very pronounced. A number of faint zones are visible below the triacontanol zone and the point of application is coloured blue.

TESTS

Melting point (*2.2.15*)

80 °C to 88 °C.

Melt the substance to be examined carefully on a water-bath before introduction into the capillary tubes. Allow the tubes to stand in the refrigerator for 24 h or at 0 °C for 2 h.

Acid value

2 to 7.

To 2.000 g (*m* g) in a 250 mL conical flask fitted with a reflux condenser add 40 mL of *xylene R* and a few glass beads. Heat with stirring until the substance is completely dissolved. Add 20 mL of *ethanol (96 per cent) R* and 1 mL of *bromothymol blue solution R3* and titrate the hot solution with 0.5 M alcoholic potassium hydroxide until a green colour persisting for at least 10 s is obtained (n_1 mL). Carry out a blank test (n_2 mL). Calculate the acid value using the following expression:

$$\frac{28.05\left(n_1 - n_2\right)}{m}$$

Saponification value

78 to 95.

To 2.000 g (*m* g) in a 250 mL conical flask fitted with a reflux condenser add 40 mL of *xylene R* and a few glass beads. Heat with stirring until the substance is completely dissolved. Add 20 mL of *ethanol (96 per cent) R* and 20.0 mL of 0.5 M alcoholic potassium hydroxide. Boil under a reflux condenser for 3 h. Add 1 mL of *phenolphthalein solution R1* and titrate the hot solution immediately with *0.5 M hydrochloric acid* until the red colour disappears. Repeat the heating and titration until the colour no longer reappears on heating (n_3 mL). Carry out a blank test (n_4 mL). Calculate the saponification value using the following expression:

www.webofpharma.com

https://thuathuocngocanh.com/

$$\frac{28.05\left(n_4 - n_3\right)}{m}$$

Total ash (*2.4.16*)

Maximum 0.25 per cent, determined on 2.0 g.

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carrageenan

General Notices

(Ph. Eur. monograph 2138)

Ph Eur

DEFINITION

Polysaccharides extracted from different Rhodophyceae with boiling water or aqueous alkali solutions. Carrageenan is separated by alcohol precipitation, potassium chloride precipitation, gel pressing, drum drying or freezing. The alcohol used during separation and purification is generally 2-propanol. The main components are potassium, sodium, calcium or magnesium salts of the sulfate esters of D-galactose and 3,6-anhydro-D-galactose copolymers. They exist in different proportions depending on the biological origin of the polymer.

The prevalent copolymers are designated as κ-, ι- and λ-carrageenan.

CHARACTERS

Appearance

Yellowish, brownish, or white or almost white powder.

Solubility

Soluble in water giving a viscous or colloidal solution, insoluble in organic solvents.

IDENTIFICATION

A. Prepare a 20 g/L dispersion and heat in a water-bath at 80 °C. Mix 1 volume of this solution and about 4 volumes of *water R* and add 2-3 drops of a 0.5 g/L solution of *methylene blue R* in *ethanol (96 per cent) R*. A blue precipitate is formed.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Prepare a 2 g/L solution of the substance to be examined; cast 4.5 mL of the solution into a plastic flat-bottomed weighing boat about 35 mm in diameter and allow to dry completely in an air-flow oven at 60 °C until a film, about 10 µm thick, is obtained (about 4 h).

Carrageenan has strong, broad absorption bands, typical of all polysaccharides, in the 1000-1100 cm^{-1} region. Absorption maxima are 1065 cm^{-1} and 1020 cm^{-1} for gelling and non-gelling types, respectively. Other characteristic absorption bands and their intensities relative to the absorbance at 1050 cm^{-1} are shown in Table 2138.-1.

Table 2138.-1. – *Characteristic absorption bands for carrageenan identification by infrared absorption spectrophotometry*

www.webofpharma.com

https://thuathuocngocanh.com/

Wavenumber (cm^{-1})	Molecular structure	Absorbance relative to the absorbance at 1050 cm^{-1}		
		κ	ι	λ
1220 - 1260	Ester sulfate	0.7 - 1.2	1.2 -2.0	1.4 - 2.0
928 - 933	3,6-Anhydro-D-galactose	0.3 - 0.6	0.2 - 0.5	≤ 0.2
840 - 850	Galactose-4-sulfate	0.3 - 0.5	0.2 - 0.4	-
825 - 830	Galactose-2-sulfate	-	-	0.2 - 0.4
810 - 820	Galactose-6-sulfate	-	-	0.1 - 0.3
800 - 805	3,6-Anhydro-D-galactose-2-sulfate	≤ 0.2	0.2 - 0.4	-

Table 2138.-1 shows absorbance ratios corresponding to copolymer types isolated from carrageenans. Native extracts of carrageenan from most cold-water seaweed species comprise κ-, ι- and λ-structures from the natural mix of haploid and diploid plants. Such extracts exhibit, in practice, the characteristic absorbance peaks of κ-, ι- and λ-structures and yield absorbance ratios somewhere between the above-mentioned individual ranges.

TESTS

Viscosity (*2.2.10*)

Minimum 5 mPa·s. Heat a 15 g/L dispersion (dried substance) at 80 °C for at least 15 min to dissolve. Compensate for any loss of water by evaporation, allow to cool to 75 °C and carry out the test at this temperature.

Arsenic (*2.4.27*)

Maximum 3.0 ppm.

Cadmium (*2.4.27*)

Maximum 2.0 ppm.

Lead (*2.4.27*)

Maximum 5.0 ppm.

Mercury (*2.4.27*)

Maximum 1.0 ppm.

Loss on drying (*2.2.32*)

Maximum 12.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Total ash (*2.4.16*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 40.0 per cent.

Ash insoluble in hydrochloric acid (*2.8.1*)

Maximum 2.0 per cent.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for carrageenan used as viscosity-increasing agent.

Gel formation

Prepare a 20 g/L dispersion and heat in a water-bath at 80 °C (solution A). Allow to cool; it becomes more viscous upon cooling and may form a gel.

To 10 mL of solution A, while still hot, add 4 drops of a 100 g/L solution of *potassium chloride R*, mix and allow to cool. A ‘brittle’ gel indicates a carrageenan of a predominantly κ-type; an ‘elastic’ gel indicates a predominantly ι-type; if the solution does not form a gel, the carrageenan is of a predominantly λ-type; a weak or pourable gel obtained on cooling indicates a carrageenan comprising a mixture of κ- and λ-types, which can be confirmed by infrared absorption spectrophotometry.

Viscosity

(see Tests).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carteolol Eye Drops

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Carteolol Eye Drops are a sterile solution of Carteolol Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of carteolol hydrochloride, $C_{16}H_{24}N_2O_3,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the eye drops with *water*, if necessary, to contain 0.5% w/v of Carteolol Hydrochloride.

(2) 0.5% w/v of *carteolol hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 20 volumes of *methanol* and 50 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://nhathuocngocanh.com/

Acidity

pH, 6.2 to 7.2, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the eye drops with the mobile phase to contain 0.20% w/v of Carteolol Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC-Pack ODS-A is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate such that the retention time of carteolol hydrochloride is about 14 minutes (1 mL per minute may be suitable).

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 252 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *methanol*, 20 volumes of *acetonitrile* and 79 volumes of a 0.282% w/v solution of *sodium hexanesulfonate*.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (2) the *column efficiency*, determined on the principal peak, is at least 6000 *theoretical plates* per metre.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of not more than one such peak is greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of all such peaks is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the eye drops to contain 0.002% w/v of Carteolol Hydrochloride.

(2) 0.002% w/v of *carteolol hydrochloride BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 252 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1.0 g of *potassium dihydrogen orthophosphate* in a mixture of 80 mL of *acetonitrile* and 400 mL of *water*.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (2) the *column efficiency*, determined on the principal peak, is at least 6000 *theoretical plates* per metre.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{24}N_2O_3$,HCl in the eye drops using the declared content of $C_{16}H_{24}N_2O_3$,HCl in *carteolol hydrochloride BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

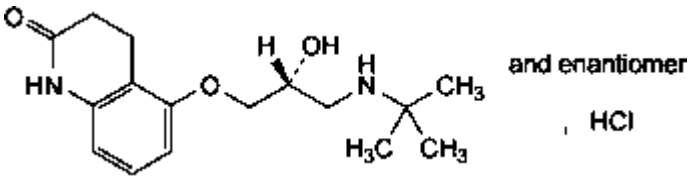
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carteolol Hydrochloride

General Notices

(Ph. Eur. monograph 1972)



$C_{16}H_{25}N_2O_3Cl$ 328.8 *51781-21-6*

Action and use

Beta-adrenoceptor antagonist.

Preparation

Carteolol Eye Drops

Ph Eur

DEFINITION

5-[(2*RS*)-3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white crystals or crystalline powder.

Solubility

Soluble in water, sparingly soluble in methanol, slightly soluble in ethanol 96 per cent, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *Ph. Eur. reference spectrum of carteolol hydrochloride*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.300 g in *water R* and dilute to 10 mL with the same solvent.

pH (*2.2.3*)

5.0 to 6.0.

Dissolve 0.250 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 10 mg of *carteolol for system suitability CRS* in the mobile phase and dilute to 5 mL with the mobile phase.

Reference solution (d) Dilute 5.0 mL of reference solution (b) to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 1 volume of *methanol R2*, 20 volumes of *acetonitrile R* and 79 volumes of a 2.82 g/L solution of *sodium hexanesulfonate R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 252 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *carteolol for system suitability CRS* to identify the peak due to impurity H.

www.webofpharma.com

https://thuocngocanh.com/

System suitability:

— the chromatogram obtained with reference solution (c) is similar to the chromatogram provided with *carteolol for system suitability CRS*; the peaks due to impurity H and carteolol show base-line separation;

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (d);

— *number of theoretical plates*: minimum 6000, calculated for the principal peak in the chromatogram obtained with reference solution (a).

Limits:

— *impurity H*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 60 mL of *ethanol (96 per cent) R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.88 mg of $C_{16}H_{25}N_2O_3Cl$.

STORAGE

In an airtight container.

IMPURITIES

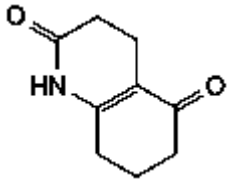
Specified impurities H.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

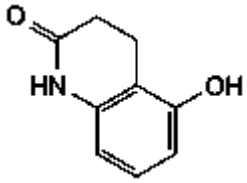
www.webofpharma.com

https://thuocngocanh.com/

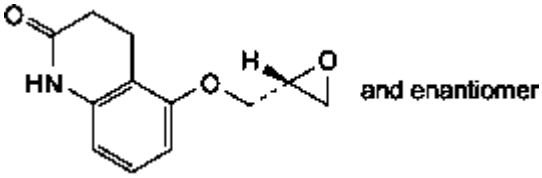
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, I.



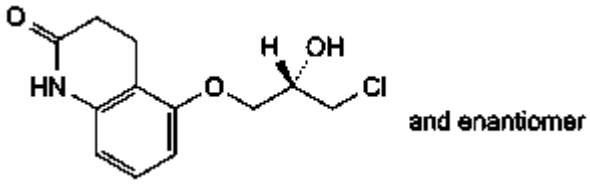
A. 4,6,7,8-tetrahydroquinoline-2,5(1*H*,3*H*)-dione,



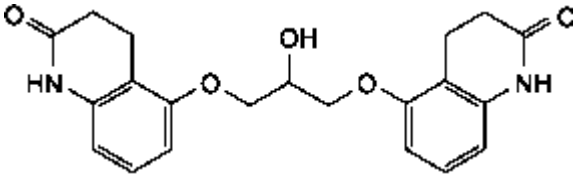
B. 5-hydroxy-3,4-dihydroquinolin-2(1*H*)-one,



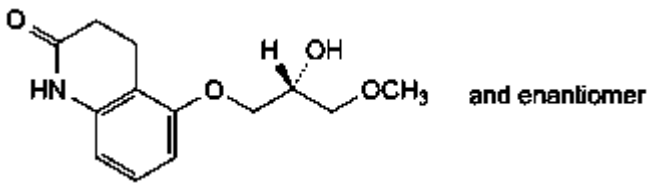
C. 5-[[(2*RS*)-oxiran-2-yl]methoxy]-3,4-dihydroquinolin-2(1*H*)-one,



D. 5-[(2*RS*)-3-chloro-2-hydroxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one,



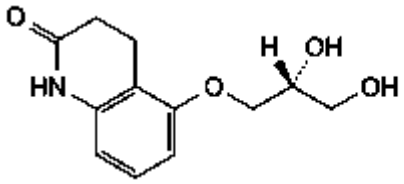
E. 5,5′-[(2-hydroxypropan-1,3-diyl)bis(oxy)]bis(3,4-dihydroquinolin-2(1*H*)-one),



F. 5-[(2*RS*)-2-hydroxy-3-methoxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one,

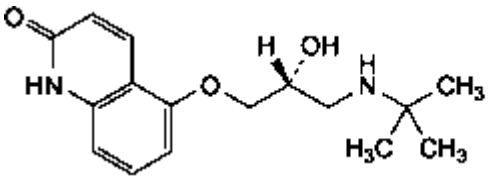
www.webofpharma.com

https://thuocngocanh.com/



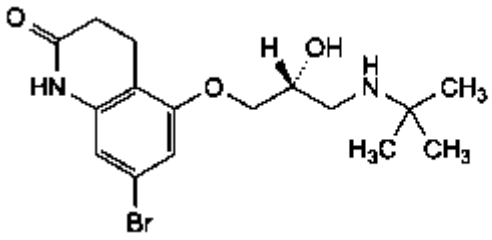
and enantiomer

G. 5-[(2*RS*)-2,3-dihydroxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one,



and enantiomer

H. 5-[(2*RS*)-3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]quinolin-2(1*H*)-one,



and enantiomer

I. 7-bromo-5-[(2*RS*)-3-[(1,1-(dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydroquinolin-2(1*H*)-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

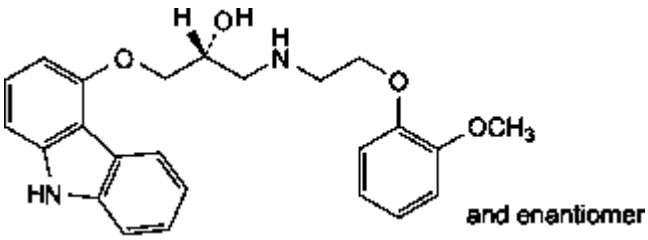
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carvedilol

General Notices

(Ph. Eur. monograph 1745)



$C_{24}H_{26}N_2O_4$ 406.5 *72956-09-3*

Action and use

Beta-adrenoceptor antagonist; arteriolar vasodilator.

Preparation

Carvedilol Tablets

Ph Eur

DEFINITION

(2*RS*)-1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent). It is practically insoluble in dilute acids.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison carvedilol CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in 2-propanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of carvedilol impurity C CRS in 5.0 mL of the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 4.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of carvedilol for system suitability CRS (containing impurities A and D) in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.150 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 55 °C.

Mobile phase Dissolve 1.77 g of potassium dihydrogen phosphate R in water R and dilute to 650 mL with the same solvent; adjust to pH 2.0 with phosphoric acid R and add 350 mL of acetonitrile R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Run time 6 times the retention time of carvedilol.

Identification of impurities Use the chromatogram supplied with carvedilol for system suitability CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and D; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to carvedilol (retention time = about 4 min): impurity A = about 0.5; impurity C = about 2.9; impurity D = about 3.8.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to impurity A and carvedilol in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity C in the chromatogram obtained with reference solution (b).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 2.0;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.02 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than C*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 40.65 mg of $C_{24}H_{26}N_2O_4$.

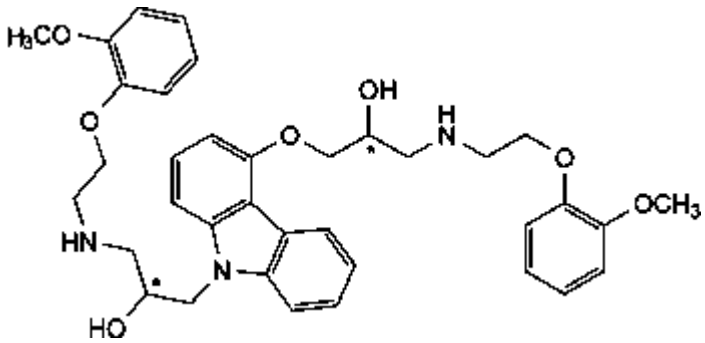
IMPURITIES

Specified impurities *A, C, D*.

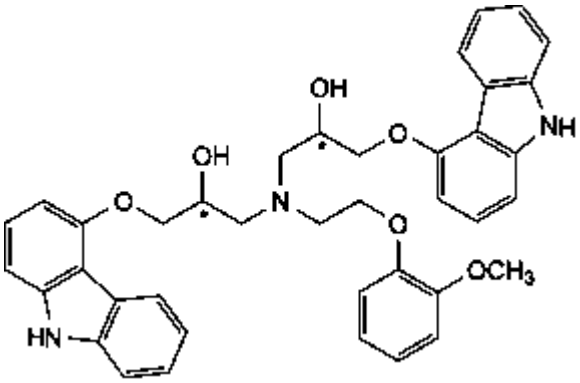
www.webofpharma.com

https://thuocngocanh.com/

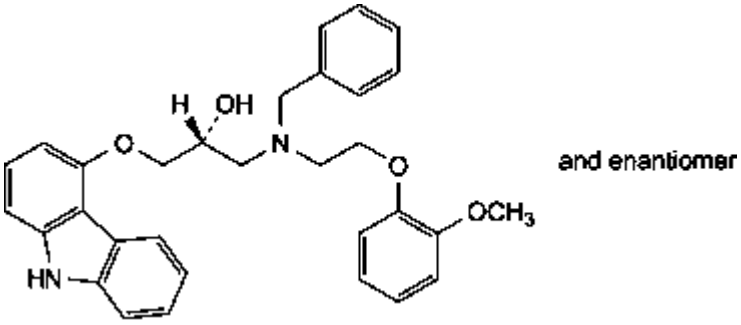
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. 1-[[9-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]-9*H*-carbazol-4-yl]oxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol,



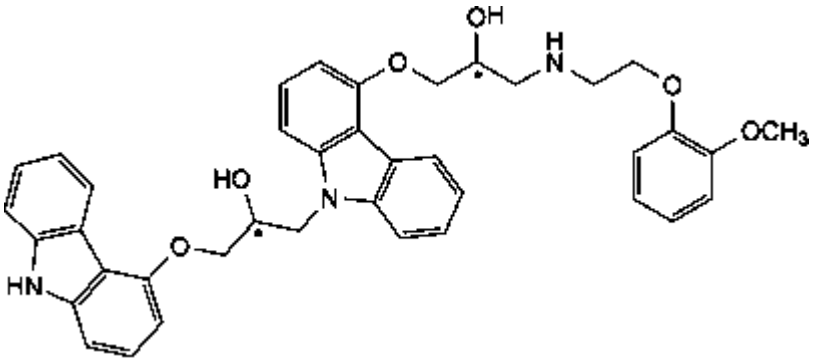
B. 1,1′-[[2-(2-methoxyphenoxy)ethyl]nitrilo]bis[3-(9*H*-carbazol-4-yloxy)propan-2-ol],



C. (2*RS*)-1-[benzyl[2-(2-methoxyphenoxy)ethyl]amino]-3-(9*H*-carbazol-4-yloxy)propan-2-ol,

www.webofpharma.com

https://thuvienthuocngocanh.com/



D. 1-(9*H*-carbazol-4-yloxy)-3-[4-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propoxy]-9*H*-carbazol-9-yl]propan-2-ol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Carvedilol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist; arteriolar vasodilator.

DEFINITION

Carvedilol Tablets contain Carvedilol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of carvedilol, $C_{24}H_{26}N_2O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of powdered tablets containing 50 mg of Carvedilol with 20 mL of *dichloromethane* for 15 minutes. Filter (a GF/C filter is suitable), evaporate the filtrate to dryness under a stream of nitrogen and dry at 60° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *infrared absorption spectrum* of *carvedilol BPCRS* prepared in the same manner. Compare the spectra between 1500 cm^{-1} and 400 cm^{-1}.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a 0.7% v/v solution of *hydrochloric acid* adjusted to pH 1.5 using *sodium hydroxide (50%)*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary to produce a solution expected to contain 0.00035% w/v of Carvedilol, at 285 nm and 380 nm, Appendix II B, using dissolution medium in the reference cell.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of 0.0028% w/v of *carvedilol BPCRS* in *methanol* to 10 volumes with the dissolution medium. Measure the *absorbance* at 285 nm and 380 nm, using dissolution medium in the reference cell.

Calculate the corrected absorbance from the following expression:

$$A_{CORR} = A_{285} - A_{380}$$

Where:

A_{CORR} = the corrected absorbance

A_{285} = the absorbance at 285 nm

A_{380} = the absorbance at 380 nm

DETERMINATION OF CONTENT

Calculate the total content of carvedilol, $C_{24}H_{26}N_2O_4$, in the medium from the corrected absorbances obtained and using the declared content of $C_{24}H_{26}N_2O_4$, in *carvedilol BPCRS*.

LIMITS

The amount of carvedilol released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare a mixture of 1 volume of 1M *hydrochloric acid* and 9 volumes of *methanol* (diluent).

(1) Shake a quantity of the powdered tablets containing 25 mg of Carvedilol in 10 mL of *water* for 20 minutes. Add 70 mL of diluent and mix with the aid of ultrasound for 30 minutes. Dilute to 100 mL with diluent, mix and centrifuge. Dilute 1 volume of the supernatant liquid to 2 volumes with *water* and filter (a 0.45-µm filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with diluent. Dilute 1 volume of this solution to 10 volumes with diluent.

(3) Dissolve 3.125 mg of *carvedilol impurity C EPCRS* in a solution consisting of 1 volume of *water* and 9 volumes of diluent. Dilute to 250 mL with *methanol (50%)*. Dilute 10 mL of this solution to 100 mL with a solution consisting of 1 volume of diluent and 1 volume of *water*. Dilute 1 volume of this solution to 50 volumes with a solution consisting of 1 volume of diluent and 1 volume of water.

(4) 0.1% w/v of *carvedilol for system suitability EPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (3 µm) (Hypersil MOS-1 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

Buffer solution

10 volumes of *triethylamine* and 500 volumes of a 0.14% w/v solution of *potassium dihydrogen phosphate*, adjusted to pH 3.0 using *orthophosphoric acid*.

Mobile phase A 75 volumes of a 0.69% w/v solution of *sodium dodecyl sulfate* in buffer solution and 360 volumes of *acetonitrile* diluted to 1000 volumes with *water*.

Mobile phase B 75 volumes of a 0.69% w/v solution of *sodium dodecyl sulfate* in buffer solution and 450 volumes of *acetonitrile* diluted to 1000 volumes with *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-25	100→0	0→100	linear gradient
25-45	0	100	isocratic
45-46	0→100	100→0	linear gradient
46-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to carvedilol (retention time about 12 minutes) are: impurity A, about 2.6; impurity C, about 2.5; impurity D, about 2.7.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (4), the *peak-to-valley* ratio is at least 3.5, where H_p is the height above the baseline of the peak due to impurity A and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity D;

in the chromatogram obtained with solution (3), the *signal-to-noise* ratio of the peak due to impurity C is at least 10.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity A using the chromatogram obtained with solution (4). Multiply the area of this peak by a correction factor of 2.0

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.02%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any *secondary peaks*, excluding the peak due to impurity C, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the powdered tablets containing 31.25 mg of Carvedilol in 150 mL for 20 minutes and mix with the aid of ultrasound for 30 minutes. Dilute to 250 mL and filter (a 0.7-µm glass microfilter is suitable).
(2) 0.0125% w/v of *carvedilol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil 100-C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 285 nm.
(f) Inject 160 µL of each solution.

MOBILE PHASE

50 volumes of *methanol* and 50 volumes of 0.1M *orthophosphoric acid* adjusted to pH 2.0 with 0.1M *potassium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to carvedilol is between 0.8 and 1.8.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{26}N_2O_4$ in the tablets using the declared content of $C_{24}H_{26}N_2O_4$ in *carvedilol BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C and D listed under Carvedilol.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

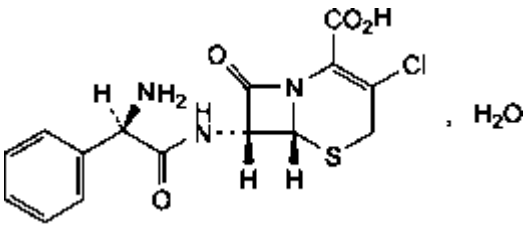
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefaclor

General Notices

(Ph. Eur. monograph 0986)



$C_{15}H_{14}ClN_3O_4S,H_2O$ 385.8 *70356-03-5*

Action and use

Cephalosporin antibacterial.

Preparations

Cefaclor Capsules

Cefaclor Oral Suspension

Cefaclor Prolonged-release Tablets

Ph Eur

DEFINITION

(6*R*,7*R*)-7-[[(2*R*)-2-Amino-2-phenylacetyl]amino]-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent of $C_{15}H_{14}ClN_3O_4S$ (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Slightly soluble in water, practically insoluble in methanol and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefaclor CRS*.

TESTS

pH (*2.2.3*)

3.0 to 4.5.

Suspend 0.250 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 101 to + 111 (anhydrous substance).

Dissolve 0.250 g in a 10 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in 10.0 mL of a 2.7 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Reference solution (a) Dissolve 2.5 mg of *cefaclor CRS* and 5.0 mg of *delta-3-cefaclor CRS* (impurity D) in 100.0 mL of a 2.7 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a 2.7 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 7.8 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 4.0 with *phosphoric acid R*;

— *mobile phase B*: mix 450 mL of *acetonitrile R* with 550 mL of mobile phase A;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	95 → 75	5 → 25
30 - 45	75 → 0	25 → 100
45 - 55	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

System suitability Reference solution (a):

— *resolution*: minimum 2 between the peaks due to cefaclor and impurity D; if necessary, adjust the acetonitrile content in the mobile phase;

— *symmetry factor*: maximum 1.2 for the peak due to cefaclor; if necessary, adjust the acetonitrile content in the mobile phase.

Limits:

— *any impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Water (*2.5.12*)

3.0 per cent to 6.5 per cent, determined on 0.200 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 15.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 15.0 mg of *cefaclor CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 3.0 mg of *cefaclor CRS* and 3.0 mg of *delta-3-cefaclor CRS* (impurity D) in the mobile phase and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Add 220 mL of *methanol R* to a mixture of 780 mL of *water R*, 10 mL of *triethylamine R* and 1 g of *sodium pentanesulfonate R*, then adjust to pH 2.5 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL.

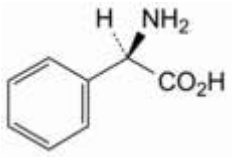
System suitability:

— *resolution*: minimum 2.5 between the peaks due to cefaclor and impurity D in the chromatogram obtained with reference solution (b); if necessary, adjust the concentration of methanol in the mobile phase;

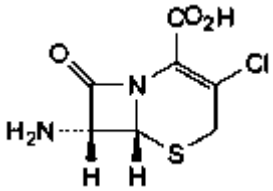
— *symmetry factor*: maximum 1.5 for the peak due to cefaclor in the chromatogram obtained with reference solution (b);

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections of reference solution (a).

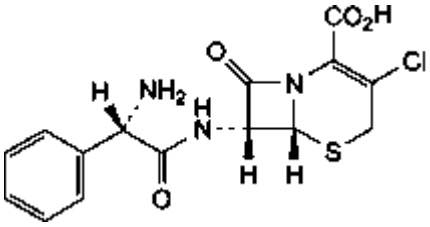
IMPURITIES



A. (2*R*)-2-amino-2-phenylacetic acid (phenylglycine),



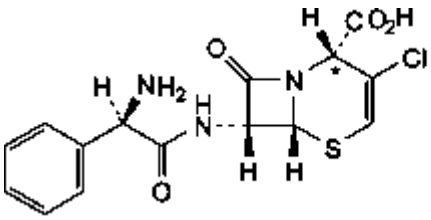
B. (6*R*,7*R*)-7-amino-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



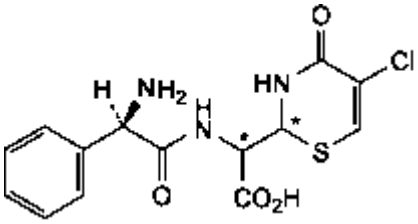
C. (6*R*,7*R*)-7-[[(2*S*)-2-amino-2-phenylacetyl]amino]-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

www.webofpharma.com

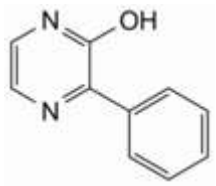
https://thuocngocanh.com/



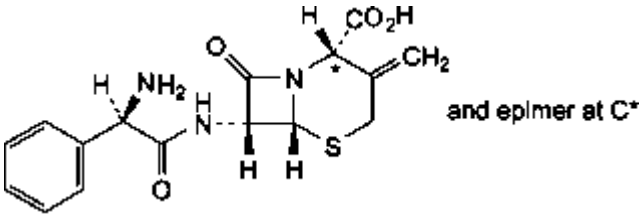
D. (2*R*,6*R*,7*R*)- and (2*S*,6*R*,7*R*)-7-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3-chloro-8-oxo-5-thia- 1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid (delta-3-cefaclor),



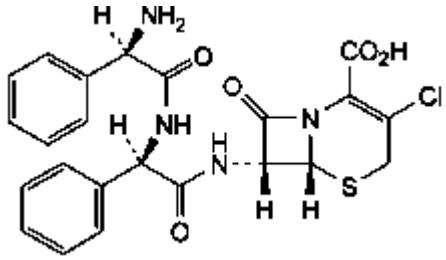
E. 2-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-(5-chloro-4-oxo-3,4-dihydro-2*H*-1,3-thiazin-2-yl)acetic acid,



F. 3-phenylpyrazin-2-ol,



G. (2*R*,6*R*,7*R*)- and (2*S*,6*R*,7*R*)-7-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3-methylene-8-oxo-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic acid (isocefalexine),



H. (6*R*,7*R*)-7-[[(2*R*)-2-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-phenylacetyl]amino]-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (*N*-phenylglycyl cefaclor).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefaclor Capsules

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefaclor Capsules contain Cefaclor.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of anhydrous cefaclor, $C_{15}H_{14}ClN_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing the equivalent of 0.3 g of anhydrous cefaclor with 100 mL of *water*, filter and dilute 1 mL of the filtrate to 100 mL with *water*. The *light absorption*, Appendix II B, in the range 190 nm to 310 nm, of the final solution exhibits a maximum only at 264 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium, filter and dilute the filtered solution, if necessary, with sufficient *water* to produce a solution expected to contain the equivalent of about 0.025% w/v of anhydrous cefaclor. Measure the *absorbance* of the filtered sample at the maximum at 264 nm, Appendix II B, using *water* in the reference cell.

(2) Measure the *absorbance* of a 0.025% w/v solution of *cefaclor BPCRS* in *water* using *water* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of anhydrous cefaclor, $C_{15}H_{14}ClN_3O_4S$, in the medium from the absorbances obtained and using the declared content of $C_{15}H_{14}ClN_3O_4S$ in *cefaclor BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a 0.27% w/v solution of *sodium dihydrogen orthophosphate* which has been adjusted to pH 2.5, if necessary, with *orthophosphoric acid* (solution A). The solutions should be freshly prepared.

(1) Shake a quantity of the contents of the capsules containing the equivalent of 0.5 g of anhydrous cefaclor with 200 mL of solution A, add sufficient of solution A to produce 250 mL and filter.

(2) 0.002% w/v of *cefaclor BPCRS*.

(3) 0.0025% w/v of *cefaclor BPCRS* and 0.005% w/v of *delta-3-cefaclor BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS-2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.78% w/v solution of *sodium dihydrogen orthophosphate* adjusted to pH 4.0 with *orthophosphoric acid*.

Mobile phase B Mix 450 volumes of *acetonitrile* with 550 volumes of mobile phase A.

Equilibrate the column with a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A for at least 15 minutes. Inject the solutions and carry out the following gradient elution.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 → 30	95 → 75	5 → 25	linear gradient
30 → 45	75 → 0	25 → 100	linear gradient
45 → 55	0	100	isocratic
55 → 70	0 → 95	100 → 5	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefaclor and delta-3-cefaclor is at least 2.0. If necessary, adjust the proportion of *acetonitrile* in the mobile phase.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered, mixed contents of 20 capsules containing the equivalent of 75 mg of anhydrous cefaclor with the mobile phase, add sufficient mobile phase to produce 250 mL and filter.
(2) 0.03% w/v of *cefaclor BPCRS* in the mobile phase.
(3) 0.03% w/v of each of *cefaclor BPCRS* and *delta-3-cefaclor BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Beckman Ultrasphere ODS and Supelcosil LC-18-DB are suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 265 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 1 g of *sodium pentanesulfonate* in a mixture of 780 mL of *water* and 10 mL of *triethylamine*, adjust the pH to 2.5 using *orthophosphoric acid*, add 220 mL of *methanol* and mix.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefaclor and delta-3-cefaclor is at least 2.5 and the *symmetry factor* of the peak due to cefaclor is at most 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{14}ClN_3O_4S$ in the capsules from the chromatograms obtained and using the declared content of $C_{15}H_{14}ClN_3O_4S$ in *cefaclor BPCRS*.

STORAGE

Cefaclor Capsules should be stored at a temperature not exceeding 30°.

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous cefaclor.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefaclor Oral Suspension

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefaclor Oral Suspension is a suspension of Cefaclor in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of Water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

STORAGE

The dry ingredients should be protected from light and stored at a temperature not exceeding 30°.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of anhydrous cefaclor, $C_{15}H_{14}ClN_3O_4S$

When freshly constituted, not more than 120.0% of the stated amount. When stored at the temperature and for the period stated on the label during which the Oral Suspension may be expected to be satisfactory for use, not less than 80.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the oral suspension containing the equivalent of 0.3 g of anhydrous cefaclor with 500 mL of *water*, filter and use the filtrate. The *light absorption*, Appendix II B, in the range 190 nm to 310 nm, of the final solution exhibits a maximum only at 264 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a 0.27% w/v solution of *sodium dihydrogen orthophosphate* which has been adjusted to pH 2.5, if necessary, with *orthophosphoric acid* (solution A). The solutions should be freshly prepared.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of the oral suspension containing the equivalent of 0.25 g of anhydrous cefaclor with 200 mL of solution A, add sufficient of solution A to produce 250 mL and filter.

(2) 0.001% w/v of *cefaclor BPCRS*.

(3) 0.0025% w/v of *cefaclor BPCRS* and 0.005% w/v of *delta-3-cefaclor BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS-2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.78% w/v solution of *sodium dihydrogen orthophosphate* adjusted to pH 4.0 with *orthophosphoric acid*.

Mobile phase B Mix 450 volumes of *acetonitrile* with 550 volumes of mobile phase A.

Equilibrate the column with a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A for at least 15 minutes. Inject the solutions and carry out the following gradient elution.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 → 30	95 → 75	5 → 25	linear gradient
30 → 45	75 → 0	25 → 100	linear gradient
45 → 55	0	100	isocratic
55 → 70	0 → 95	100 → 5	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefaclor and delta-3-cefaclor is at least 2.0. If necessary, adjust the proportion of *acetonitrile* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than 0.1 times that of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

www.webofpharma.com

https://thuathuocngocanh.com/

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the oral suspension containing the equivalent of 75 mg of anhydrous cefaclor with 200 mL of the mobile phase, add sufficient of the mobile phase to produce 250 mL and filter.

(2) 0.03% w/v of *cefaclor BPCRS* in the mobile phase.

(3) 0.03% w/v of each of *cefaclor BPCRS* and *delta-3-cefaclor BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Beckman Ultrasphere ODS and Supelcosil LC-18-DB are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 1 g of *sodium pentanesulfonate* in a mixture of 780 mL of *water* and 10 mL of *triethylamine*, adjust the pH to 2.5 using *orthophosphoric acid*, add 220 mL of *methanol* and mix.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefaclor and delta-3-cefaclor is at least 2.5 and the *symmetry factor* of the peak due to cefaclor is at most 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{15}H_{14}ClN_3O_4S$, weight in volume, using the declared content of $C_{15}H_{14}ClN_3O_4S$ in *cefaclor BPCRS*.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The Oral Suspension should be stored at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous cefaclor.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefaclor Prolonged-release Tablets

General Notices

Prolonged-release Cefaclor Tablets

Cefaclor Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefaclor Prolonged-release Tablets contain Cefaclor. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Cefaclor. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous cefaclor, $C_{15}H_{14}ClN_3O_4S$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 0.3 g of anhydrous cefaclor with 100 mL of *water*, filter and dilute 1 mL of the filtrate to 100 mL with *water*. The *light absorption*, Appendix II B, in the range 190 nm to 310 nm, of the final solution exhibits a maximum only at 264 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a 0.27% w/v solution of *sodium dihydrogen orthophosphate* which has been adjusted to pH 2.5, if necessary, with *orthophosphoric acid* (solution A). The solutions should be freshly

www.webofpharma.com

https://thuocngocanh.com/

prepared.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.75 g of anhydrous cefaclor with 200 mL of solution A, add sufficient of solution A to produce 250 mL and filter.

(2) 0.003% w/v of *cefaclor BPCRS*.

(3) 0.0025% w/v of *cefaclor BPCRS* and 0.005% w/v of *delta-3-cefaclor EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS-2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.78% w/v solution of *sodium dihydrogen orthophosphate* adjusted to pH 4.0 with *orthophosphoric acid*.

Mobile phase B Mix 450 volumes of *acetonitrile* with 550 volumes of mobile phase A.

Equilibrate the column with a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A for at least 15 minutes. Inject the solutions and carry out the following gradient elution.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 → 30	95 → 75	5 → 25	linear gradient
30 → 45	75 → 0	25 → 100	linear gradient
45 → 55	0	100	isocratic
55 → 70	0 → 95	100 → 5	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefaclor and delta-3-cefaclor is at least 2.0. If necessary, adjust the proportion of *acetonitrile* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

www.webofpharma.com

https://thuocngocanh.com/

Disregard any peak with an area less than 0.1 times that of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 75 mg of anhydrous cefaclor with 200 mL of the mobile phase, add sufficient of the mobile phase to produce 250 mL and filter.

(2) 0.03% w/v of *cefaclor BPCRS* in the mobile phase.

(3) 0.03% w/v of each of *cefaclor BPCRS* and *delta-3-cefaclor EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Beckman Ultrasphere ODS and Supelcosil LC-18-DB are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 1 g of *sodium pentanesulfonate* in a mixture of 780 mL of *water* and 10 mL of *triethylamine*, adjust the pH to 2.5 using *orthophosphoric acid*, add 220 mL of *methanol* and mix.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefaclor and delta-3-cefaclor is at least 2.5 and the *symmetry factor* of the peak due to cefaclor is at most 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{14}ClN_3O_4S$ in the tablets from the chromatograms obtained and using the declared content of $C_{15}H_{14}ClN_3O_4S$ in *cefaclor BPCRS*.

STORAGE

Cefaclor Prolonged-release Tablets should be stored at a temperature not exceeding 30°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous cefaclor.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefadroxil Capsules

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefadroxil Capsules contain Cefadroxil Monohydrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of anhydrous cefadroxil, $C_{16}H_{17}N_3O_5S$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel plate* (Merck silica gel 60 plates are suitable) and a mixture of 3 volumes of a 6.7% w/v solution of *ninhydrin* in *acetone*, 80 volumes of a 0.1M solution of *disodium hydrogen orthophosphate* and 120 volumes of a 0.1M solution of *citric acid* as the mobile phase. Impregnate the plate by development with a 5% v/v solution of n-*tetradecane* in *hexane*. Allow the solvent to evaporate and carry out the chromatography in the same direction as the impregnation. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) stir a quantity of the contents of the capsules containing the equivalent of 0.2 g of anhydrous cefadroxil with 100 mL of *water*, filter and use the filtrate. Solution (2) contains 0.2% w/v of *cefadroxil BPCRS* in *water*. After removal of the plate allow it to dry in air, spray with a 0.2% w/v solution of *ninhydrin* in *absolute ethanol*, heat the plate at 110° for 10 minutes and allow to cool. The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of *water* and rotating the basket at 100 revolutions per minute. Withdraw a sample of 10 mL of the medium and filter. Measure the *absorbance* of the filtered medium, diluted if necessary with *water*, at the maximum at 263 nm using *water* in the reference cell, Appendix II B. Calculate the total content of anhydrous cefadroxil, $C_{16}H_{17}N_3O_5S$, in the medium from the *absorbance* obtained from a 0.003% w/v solution of *cefadroxil BPCRS* in *water* and using the declared content of $C_{16}H_{17}N_3O_5S$ in *cefadroxil BPCRS*.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions. For solution (1) add 50 mL of the mobile phase to a quantity of the contents of the capsules containing the equivalent of 0.5 g of anhydrous cefadroxil, mix, stir magnetically for 10 minutes, filter and use the filtrate. Solution (2) contains 0.01% w/v of *cefadroxil BPCRS* in the mobile phase. Solution (3) contains 0.01% w/v of *D-α-(4-hydroxyphenyl)glycine BPCRS* (cefadroxil impurity A) in the mobile phase. Solution (4) contains 0.01% w/v of *7-aminodesacetoxycephalosporanic acid BPCRS* (cefadroxil impurity B) in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a solution prepared as described below and (c) a detection wavelength of 254 nm. For the mobile phase add 200 mL of 1M *potassium hydroxide*, 40 mL of *0.4M tetrabutylammonium hydroxide* and 80 mL of *methanol* to 1600 mL of *water*, mix, add sufficient *water* to produce 2000 mL and adjust the pH to 7.0, if necessary, with *orthophosphoric acid*. For solution (1) allow the chromatography to proceed for 6 times the retention time of the principal peak.

When the chromatograms are recorded under the conditions described above the retention time of cefadroxil is 8 to 12 minutes. If necessary, adjust the composition of the mobile phase (increasing the methanol content decreases the retention time, decreasing the methanol content increases the retention time).

The test is not valid unless the *column efficiency*, determined on the peak due to cefadroxil in the chromatogram obtained with solution (2), is at least 1500 *theoretical plates* per metre and the *symmetry factor* of the principal peak is at most 1.6.

Inject solution (2) five times. The test is not valid unless the relative standard deviation of the area of the principal peak is at most 2.0%.

In the chromatogram obtained with solution (1) the area of any peak corresponding to cefadroxil impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%), the area of any peak corresponding to cefadroxil impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1%) and the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Water

The contents of the capsules contain not more than 7.0% w/w of water, Appendix IX C. Use 0.5 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the mixed contents of 20 capsules containing the equivalent of 0.2 g of anhydrous cefadroxil with 150 mL of a phosphate buffer prepared by dissolving 13.6 g of *potassium dihydrogen orthophosphate* in sufficient *water* to produce 2000 mL and adjusting the pH, if necessary, to 5.0 with 10M *potassium hydroxide* for 5 minutes. Add sufficient of the buffer solution to produce 200 mL and filter. Solution (2) contains 0.1% w/v of *cefadroxil BPCRS* in the buffer solution. Solution (3) contains 0.005% w/v of *cefadroxil BPCRS* and 0.05% w/v of *amoxicillin trihydrate BPCRS* in the buffer solution.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm or 10 µm) (Hypersil ODS is suitable), (b) as the mobile phase at a flow rate of 1.0 mL per

www.webofpharma.com

https://thuocngocanh.com/

minute a mixture of 4 volumes of *acetonitrile* and 96 volumes of a 0.272% w/v solution of *potassium dihydrogen orthophosphate* and (c) a detection wavelength of 254 nm.

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to cefadroxil and amoxicillin is at least 5.0. If necessary, adjust the *acetonitrile* content in the mobile phase.

Calculate the content of $C_{16}H_{17}N_3O_5S$ in the capsules using the declared content of $C_{16}H_{17}N_3O_5S$ in *cefadroxil BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous cefadroxil.

© Crown Copyright 2022

www.webofpharma.com

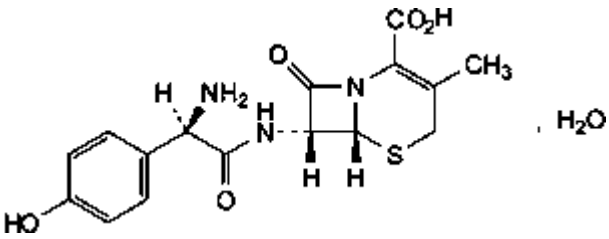
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefadroxil Monohydrate

General Notices

(Ph. Eur. monograph 0813)



$C_{16}H_{17}N_3O_5S,H_2O$ 381.4 *66592-87-8*

Action and use

Cephalosporin antibacterial.

Preparations

Cefadroxil Capsules

Cefadroxil Oral Suspension

Ph Eur

DEFINITION

(6*R*,7*R*)-7-[[(2*R*)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Slightly soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefadroxil CRS*.

TESTS

pH (*2.2.3*)

4.0 to 6.0.

Suspend 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 165 to + 178 (anhydrous substance).

Dissolve 0.500 g in *water R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 10.0 mg of *D-α-(4-hydroxyphenyl)glycine CRS* (impurity A) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 10.0 mg of *7-aminodesacetoxycephalosporanic acid CRS* (impurity B) in *phosphate buffer solution pH 7.0 R5* and dilute to 10.0 mL with the same buffer solution.

Reference solution (c) Dilute 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) to 100.0 mL with mobile phase A.

Reference solution (d) Dissolve 10 mg of *dimethylformamide R* and 10 mg of *dimethylacetamide R* in mobile phase A and dilute to 10.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase A.

Reference solution (e) Dilute 1.0 mL of reference solution (c) to 25.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: *phosphate buffer solution pH 5.0 R*,

— *mobile phase B*: *methanol R2*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	98	2
1 - 20	98 → 70	2 → 30

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (c), (d) and (e).

Relative retention With reference to cefadroxil (retention time = about 6 min): dimethylformamide = about 0.4; dimethylacetamide = about 0.75.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to impurities A and B in the chromatogram obtained with reference solution (c),

— *signal-to-noise ratio*: minimum 10 for the 2nd peak in the chromatogram obtained with reference solution (e).

Limits:

— *impurity A*: not more than the area of the 1st peak in the chromatogram obtained with reference solution (c) (1.0 per cent),

— *any other impurity*: for each impurity, not more than the area of the 2nd peak in the chromatogram obtained with reference solution (c) (1.0 per cent),

— *total*: not more than 3 times the area of the 2nd peak in the chromatogram obtained with reference solution (c) (3.0 per cent),

— *disregard limit*: 0.05 times the area of the 2nd peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard the peaks due to dimethylformamide and dimethylacetamide.

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

Water (*2.5.12*)

4.0 per cent to 6.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *cefadroxil CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *cefadroxil CRS* and 50 mg of *amoxicillin trihydrate CRS* in the mobile phase and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, a 2.72 g/L solution of *potassium dihydrogen phosphate R* (4:96 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

System suitability Reference solution (b):

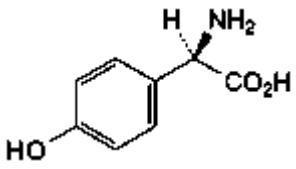
— *resolution*: minimum 5.0 between the peaks due to cefadroxil and to amoxicillin.

Calculate the percentage content of cefadroxil.

STORAGE

Protected from light.

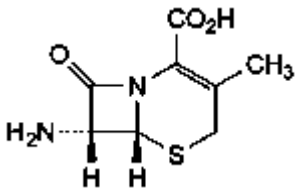
IMPURITIES



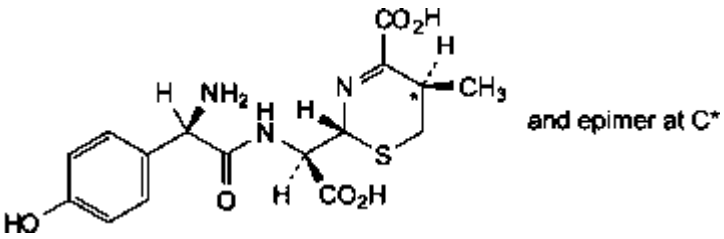
A. (2*R*)-2-amino-2-(4-hydroxyphenyl)acetic acid,

www.webofpharma.com

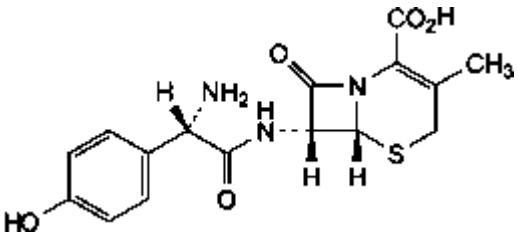
https://thuocngocanh.com/



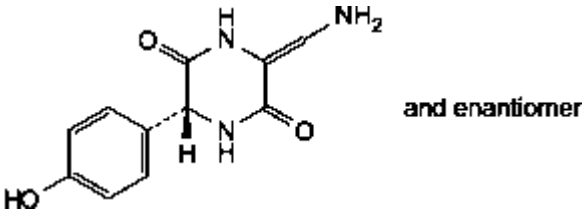
B. (6*R*,7*R*)-7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ADCA),



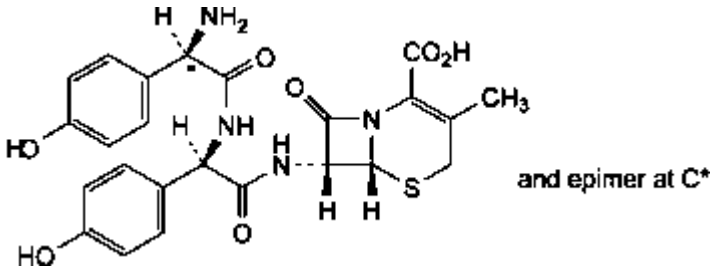
C. (2*R*,5*RS*)-2-[(*R*)-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]carboxymethyl]-5-methyl-5,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid,



D. (6*R*,7*R*)-7-[[(2*S*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (L-cefadroxil),



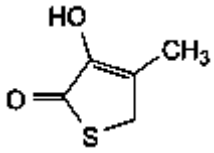
E. (6*RS*)-3-(aminomethylene)-6-(4-hydroxyphenyl)piperazine-2,5-dione,



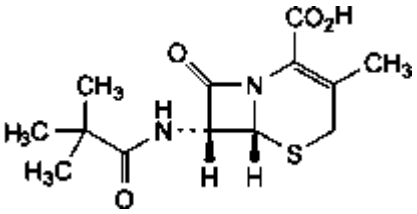
F. (6*R*,7*R*)-7-[[(2*R*)-2-[[(2*RS*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

www.webofpharma.com

https://thuvienthuocngocanh.com/



G. 3-hydroxy-4-methylthiophen-2(5*H*)-one,



H. (6*R*,7*R*)-7-[(2,2-dimethylpropanoyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ADCA pivalamide).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefadroxil Oral Suspension

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefadroxil Oral Suspension is a suspension of Cefadroxil Monohydrate in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of Water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

STORAGE

The dry ingredients should be stored at a temperature not exceeding 30°.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of anhydrous cefadroxil, $C_{16}H_{17}N_3O_5S$

When freshly constituted not more than 110.0% of the stated amount. When stored at the temperature and for the period stated on the label, during which the Oral Suspension may be expected to be satisfactory for use, not less than 90.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel plate* (Merck silica gel 60 plates are suitable) and a mixture of 3 volumes of a 6.7% w/v solution of *ninhydrin* in *acetone*, 80 volumes of a 0.1M solution of *disodium hydrogen orthophosphate* and 120 volumes of a 0.1M solution of *citric acid* as the mobile phase. Impregnate the plate by development with a 5% v/v solution of n-*tetradecane* in *hexane*. Allow the solvent to evaporate and carry out the chromatography in the same direction as the impregnation. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) dilute a volume of the oral suspension containing the equivalent of 0.2 g of anhydrous cefadroxil to 100 mL with *water*, filter and use the filtrate. Solution (2) contains 0.2% w/v of *cefadroxil BPCRS* in *water*. After removal of the plate, allow it to dry in air, spray with a 0.2% w/v solution of *ninhydrin* in *absolute ethanol*, heat the plate at 110° for 10 minutes and allow to cool. The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acidity

pH, 4.5 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute a volume of the oral suspension with sufficient of mobile phase A to produce a solution containing the equivalent of 0.1% w/v of anhydrous cefadroxil, mix, stir magnetically for 10 minutes, filter through a 0.45-µm filter and use the filtrate. Solution (2) contains 0.001% w/v of *cefadroxil BPCRS* in mobile phase A. Solution (3) contains 0.001% w/v of *D-α-(4-hydroxyphenyl)glycine BPCRS* (cefadroxil impurity A) in mobile phase A. Solution (4) contains 0.001% w/v of *7-aminodesacetoxycephalosporanic acid BPCRS* (cefadroxil impurity B) in mobile phase A.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Lichrosorb RP-18 is suitable), (b) as mobile phases A and B with a flow rate of 1 mL per minute the solutions described below and (c) a detection wavelength of 254 nm.

Mobile phase A Dissolve 5.44 g of *potassium dihydrogen orthophosphate* in 2000 mL of *water* and adjust the pH, if necessary, to 5.0 with a 1% w/v solution of *potassium hydroxide*.

Mobile phase B Add 400 mL of *acetonitrile* to 600 mL of mobile phase A and adjust the pH, if necessary, to 5.0 with a 2% v/v solution of *orthophosphoric acid*.

Inject 20 µL of each solution and record the chromatograms under the following conditions. Elute initially with mobile phase A. After 5 minutes, use linear gradient elution increasing the concentration of mobile phase B to 32% after 35 minutes. Elute isocratically for 25 minutes with a mixture of 32% of mobile phase B and 68% of mobile phase A. Carry out a linear gradient elution for 1 minute to 100% of mobile phase A and elute for a further 9 minutes with mobile phase A.

When the chromatograms are recorded under the conditions described above the retention time of cefadroxil is 14 to 20 minutes. If necessary, adjust the proportion of mobile phase A to mobile phase B to achieve the stated retention time.

The test is not valid unless the *column efficiency*, determined on the peak due to cefadroxil in the chromatogram obtained with solution (2), is at least 2000 *theoretical plates* per metre and the *symmetry factor* of the principal peak is at most 1.5.

Inject solution (2) five times. The test is not valid unless the relative standard deviation of the area of the principal peak is at most 2.0%.

In the chromatogram obtained with solution (1) the area of any peak corresponding to cefadroxil impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%), the area of any peak corresponding to cefadroxil impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1%) and the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a weighed quantity of the oral suspension containing the equivalent of 0.25 g of anhydrous cefadroxil with 250 mL of a phosphate buffer prepared by dissolving

www.webofpharma.com

https://thuocngocanh.com/

13.6 g of *potassium dihydrogen orthophosphate* in sufficient *water* to produce 2000 mL and adjusting the pH, if necessary, to 5.0 with 10M *potassium hydroxide* for 5 minutes; filter and use the filtrate. Solution (2) contains 0.1% w/v of *cefadroxil BPCRS* in the buffer solution. Solution (3) contains 0.005% w/v of *cefadroxil BPCRS* and 0.05% w/v of *amoxicillin trihydrate BPCRS* in the buffer solution.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm or 10 µm) (Hypersil ODS is suitable), (b) as the mobile phase at a flow rate of 1.0 mL per minute a mixture of 4 volumes of *acetonitrile* and 96 volumes of a 0.272% w/v solution of *potassium dihydrogen orthophosphate* and (c) a detection wavelength of 254 nm.

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to cefadroxil and amoxicillin is at least 5.0. If necessary, adjust the *acetonitrile* content in the mobile phase.

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{16}H_{17}N_3O_5S$, weight in volume, using the declared content of $C_{16}H_{17}N_3O_5S$ in *cefadroxil BPCRS*.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

Cefadroxil Oral Suspension should be kept at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous cefadroxil.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefalexin Capsules

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefalexin Capsules contain Cefalexin Monohydrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of anhydrous cefalexin, $C_{16}H_{17}N_3O_4S$

92.5 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing the equivalent of 0.5 g of anhydrous cefalexin with 1 mL of *water* and 1.4 mL of 1M *hydrochloric acid*, filter and wash the filter with 1 mL of *water*. Add slowly to the filtrate a saturated solution of *sodium acetate* until precipitation occurs. Add 5 mL of *methanol*, filter, wash the precipitate with two 1-mL quantities of *methanol* and dry the residue at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of cefalexin (*RS 049*). Retain the dried residue for use in test C.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0*.

(1) Shake a quantity of the contents of the capsules containing the equivalent of 0.2 g of anhydrous cefalexin with 25 mL, dilute to 50 mL, filter and use the filtrate.

(2) 0.4% w/v of *cefalexin BPCRS*.

(3) 0.4% w/v of each of *cefalexin BPCRS* and *cefradine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silanised silica gel* HF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

15 volumes of *acetone* and 85 volumes of a 15.4% w/v solution of *ammonium acetate*, previously adjusted to pH 6.2 with 5M *acetic acid*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuathuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

C. Mix 20 mg of the dried residue obtained in test A with 0.25 mL of a 1% v/v solution of *glacial acetic acid* and add 0.1 mL of a 1% w/v solution of *copper(II) sulfate* and 0.1 mL of 2M *sodium hydroxide*. An olive-green colour is produced.

TESTS

Disintegration

Maximum time, 15 minutes, using a 0.6% v/v solution of *hydrochloric acid* in place of *water*, Appendix XII A1.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in 2M *hydrochloric acid*.

(1) Shake a quantity of the contents of the capsules containing the equivalent of 0.25 g of anhydrous cefalexin with 10 mL, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.025% w/v of *7-aminodesacetoxycephalosporanic acid BPCRS*.

(4) 0.025% w/v of DL-*phenylglycine*.

(5) 2.5% w/v of *cefalexin BPCRS* and 0.025% w/v of each of *7-aminodesacetoxycephalosporanic acid BPCRS* and DL-*phenylglycine*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel HF precoated plate (Analtech plates are suitable). Impregnate the plate by development with a 5% v/v solution of *n-tetradecane* in *hexane*. Allow the solvent to evaporate and carry out the chromatography in the same direction as the impregnation.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it at 90° for 3 minutes; spray the hot plate with a 0.1% w/v solution of *ninhydrin* in the mobile phase, heat the plate at 90° for 15 minutes and allow to cool.

MOBILE PHASE

3 volumes of *acetone*, 80 volumes of a 7.2% w/v solution of *disodium hydrogen orthophosphate* and 120 volumes of a 2.1% w/v solution of *citric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (5) shows three clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

any spot corresponding to 7-aminodesacetoxycephalosporanic acid is not more intense than the spot in the chromatogram obtained with solution (3) (1%);

any spot corresponding to DL-phenylglycine is not more intense than the spot in the chromatogram obtained with solution (4) (1%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Shake a quantity of the powdered, mixed contents of 20 capsules containing the equivalent of 0.25 g of anhydrous cefalexin with 100 mL of *water* for 30 minutes. Add sufficient *water* to produce 250 mL, filter and dilute 25 mL of the filtrate to 50 mL.
(2) 0.05% w/v of *cefalexin BPCRS*.
(3) 0.01% w/v of each of *cefalexin BPCRS* and *cefradine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *methanol*, 5 volumes of *acetonitrile*, 10 volumes of a 1.36% w/v solution of *potassium dihydrogen orthophosphate* and 83 volumes of *water*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to cefalexin and cefradine is at least 4.0; if necessary, adjust the *acetonitrile* content of the mobile phase.

Inject solution (2) six times. The Assay is not valid unless the relative standard deviation of the area of the principal peak is at most 1.0%.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{17}N_3O_4S$ in the capsules using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS*.

STORAGE

Cefalexin Capsules should be stored at a temperature not exceeding 30°.

LABELLING

www.webofpharma.com

https://thuathuocngocanh.com/

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous cefalexin.

© Crown Copyright 2022

www.webofpharma.com

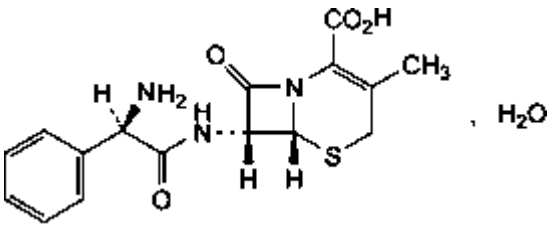
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefalexin Monohydrate

General Notices

(Ph. Eur. monograph 0708)



$C_{16}H_{17}N_3O_4S,H_2O$ 365.4 *23325-78-2*

Action and use

Cephalosporin antibacterial.

Preparations

Cefalexin Capsules

Cefalexin Oral Suspension

Cefalexin Tablets

Ph Eur

DEFINITION

(6*R*,7*R*)-7-[[(2*R*)-2-Amino-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Sparingly soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefalexin monohydrate CRS*.

TESTS

pH (*2.2.3*)

4.0 to 5.5.

Dissolve 50 mg in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 149 to + 158 (anhydrous substance).

Dissolve 0.125 g in *phthalate buffer solution pH 4.4 R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 10.0 mg of *D-phenylglycine R* in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 10.0 mg of *7-aminodesacetoxycephalosporanic acid CRS* in *phosphate buffer solution pH 7.0 R5* and dilute to 10.0 mL with mobile phase A.

Reference solution (c) Dilute 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) to 100.0 mL with mobile phase A.

Reference solution (d) Dissolve 10 mg of *dimethylformamide R* and 10 mg of *dimethylacetamide R* in mobile phase A and dilute to 10.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase A.

Reference solution (e) Dilute 1.0 mL of reference solution (c) to 20.0 mL with mobile phase A.

Reference solution (f) Dissolve 10 mg of *cefotaxime sodium CRS* in mobile phase A and dilute to 10.0 mL with mobile phase A. To 1.0 mL of this solution add 1.0 mL of the test solution and dilute to 100 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: *phosphate buffer solution pH 5.0 R*;

— *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	98	2
1 - 20	98 → 70	2 → 30

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (c), (d), (e) and (f).

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurities A and B in the chromatogram obtained with reference solution (c) and minimum 1.5 between the peaks due to cefalexin and cefotaxime in the chromatogram obtained with reference solution (f).

Limits:

— *impurity B*: not more than the area of the 2nd peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *any other impurity*: not more than the area of the 1st peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *total*: not more than 3 times the area of the 1st peak in the chromatogram obtained with reference solution (c) (3.0 per cent);

— *disregard limit*: the area of the 2nd peak in the chromatogram obtained with reference solution (e) (0.05 per cent); disregard any peaks due to dimethylformamide or dimethylacetamide.

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

Water (*2.5.12*)

4.0 per cent to 8.0 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in water R and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of cefalexin monohydrate CRS in water R and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of cefradine CRS in 20 mL of reference solution (a) and dilute to 100 mL with water R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase methanol R, acetonitrile R, 13.6 g/L solution of potassium dihydrogen phosphate R, water for chromatography R (2:5:10:83 *V/V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

System suitability Reference solution (b):

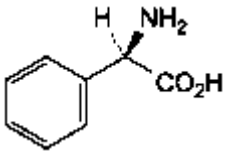
— resolution: minimum 4.0 between the peaks due to cefalexin and cefradine.

Calculate the percentage content of cefalexin monohydrate.

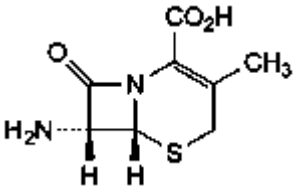
STORAGE

Protected from light.

IMPURITIES



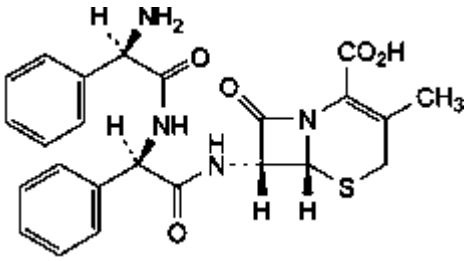
A. (2*R*)-2-amino-2-phenylacetic acid (D-phenylglycine),



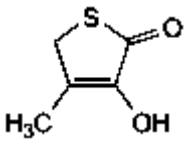
www.webofpharma.com

https://thuocngocanh.com/

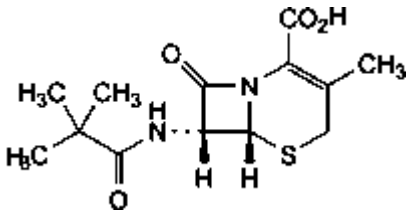
B. (6*R*,7*R*)-7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-aminodesacetoxycephalosporanic acid, 7-ADCA),



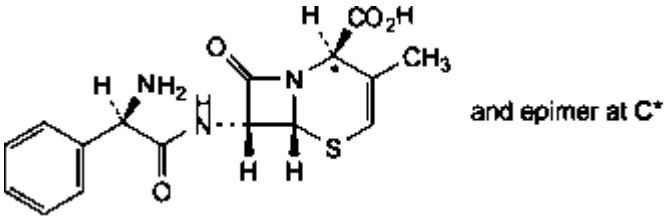
C. (6*R*,7*R*)-7-[[(2*R*)-2-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



D. 3-hydroxy-4-methylthiophen-2(5*H*)-one,



E. (6*R*,7*R*)-7-[(2,2-dimethylpropanoyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ADCA pivalamide),



F. (2*RS*,6*R*,7*R*)-7-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid (delta-2-cefalexin).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefalexin Oral Suspension

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefalexin Oral Suspension is a suspension of Cefalexin Monohydrate in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of Water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

STORAGE

The dry ingredients should be protected from light and stored at a temperature not exceeding 30°.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of anhydrous cefalexin, $C_{16}H_{17}N_3O_4S$

When freshly constituted, not more than 120.0% of the stated amount. When stored at the temperature and for the period stated on the label during which the Oral Suspension may be expected to be satisfactory for use, not less than 80.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the oral suspension containing the equivalent of 0.2 g of anhydrous cefalexin with 70 mL of *methanol*, filter, evaporate to dryness using a rotary evaporator and dissolve the residue in sufficient 0.5M *hydrochloric acid* to produce 50 mL.

(2) 0.4% w/v of *cefalexin BPCRS* in a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0*.

(3) 0.4% w/v of each of *cefalexin BPCRS* and *cefradine BPCRS* in a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silanised silica gel* HF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

www.webofpharma.com

https://thuocngocanh.com/

(e) After removal of the plate, allow it to dry and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

15 volumes of *acetone* and 85 volumes of a 15.4% w/v solution of *ammonium acetate*, previously adjusted to pH 6.2 with 5M *acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. Shake a quantity of the oral suspension containing the equivalent of 0.1 g of anhydrous cefalexin with 70 mL of *methanol*, filter and evaporate the filtrate to dryness using a rotary evaporator. Dissolve the residue in the minimum volume of a 1% v/v solution of *glacial acetic acid*, decolourise if necessary by the addition of sufficient *activated charcoal*, shake and filter. To 0.25 mL of the resulting solution add 0.1 mL of a 1% w/v solution of *copper(II) sulfate* and 0.05 mL of 2M *sodium hydroxide*. An olive-green colour is produced.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Shake a weighed quantity of the oral suspension containing the equivalent of 0.25 g of anhydrous cefalexin with 100 mL of *water* for 30 minutes. Add sufficient *water* to produce 250 mL, filter and dilute 25 mL of the filtrate to 50 mL.
(2) 0.05% w/v of *cefalexin BPCRS*.
(3) 0.01% w/v of each of *cefalexin BPCRS* and *cefradine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *methanol*, 5 volumes of *acetonitrile*, 10 volumes of a 1.36% w/v solution of *potassium dihydrogen orthophosphate* and 83 volumes of *water*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to cefalexin and cefradine is at least 4.0; if necessary, adjust the *acetonitrile* content of the mobile phase.

Inject solution (2) six times. The Assay is not valid unless the relative standard deviation of the area of the principal peak is at most 1.0%.

www.webofpharma.com

https://thuathuocngocanh.com/

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{16}H_{17}N_3O_4S$, weight in volume, using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS*.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The Oral Suspension should be stored at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous cefalexin.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefalexin Tablets

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefalexin Tablets contain Cefalexin Monohydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous cefalexin, $C_{16}H_{17}N_3O_4S$

92.5 to 110.0% of the stated amount.

IDENTIFICATION

Remove any coating. Shake a quantity of the powdered tablet cores containing the equivalent of 0.5 g of anhydrous cefalexin with 1 mL of *water* and 1.4 mL of 1M *hydrochloric acid*, add 0.1 g of *activated charcoal*, shake, filter and wash the filter with 1 mL of *water*. Add slowly to the filtrate a saturated solution of *sodium acetate* until precipitation occurs. Add 5 mL of *methanol*, filter and wash the precipitate with two 1-mL quantities of *methanol*. The residue, after drying at a pressure not exceeding 0.7 kPa, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of cefalexin *(RS 049)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0*.

(1) Shake 0.2 g with 25 mL, dilute to 50 mL, filter and use the filtrate.

(2) 0.4% w/v of *cefalexin BPCRS*.

(3) 0.4% w/v of each of *cefalexin BPCRS* and *cefradine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silanised silica gel* HF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

15 volumes of *acetone* and 85 volumes of a 15.4% w/v solution of *ammonium acetate*, previously adjusted to pH 6.2 with 5M *acetic acid*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

C. Mix 20 mg with 0.25 mL of a 1% v/v solution of *glacial acetic acid* and add 0.1 mL of a 1% w/v solution of *copper(II) sulfate* and 0.1 mL of 2M *sodium hydroxide*. An olive-green colour is produced.

TESTS

Disintegration

Maximum time, 30 minutes, Appendix XII A1.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in 2M *hydrochloric acid*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.25 g of anhydrous cefalexin with 10 mL, filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.025% w/v of *7-aminodesacetoxycephalosporanic acid BPCRS*.
(4) 0.025% w/v of DL-*phenylglycine*.
(5) 2.5% w/v of *cefalexin BPCRS* and 0.025% w/v of each of *7-aminodesacetoxycephalosporanic acid BPCRS* and DL-*phenylglycine*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel HF precoated plate (Analtech plates are suitable). Impregnate the plate by development with a 5% v/v solution of *n-tetradecane* in *hexane*. Allow the solvent to evaporate and carry out the chromatography in the same direction as the impregnation.
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry it at 90° for 3 minutes; spray the hot plate with a 0.1% w/v solution of *ninhydrin* in the mobile phase, heat the plate at 90° for 15 minutes and allow to cool.

MOBILE PHASE

3 volumes of *acetone*, 80 volumes of a 7.2% w/v solution of *disodium hydrogen orthophosphate* and 120 volumes of a 2.1% w/v solution of *citric acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (5) shows three clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuvienthuocngocanh.com/

any spot corresponding to 7-aminodesacetoxycephalosporanic acid is not more intense than the spot in the chromatogram obtained with solution (3) (1%);

any spot corresponding to DL-phenylglycine is not more intense than the spot in the chromatogram obtained with solution (4) (1%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.25 g of anhydrous cefalexin with 100 mL of *water* for 30 minutes. Add sufficient *water* to produce 250 mL, filter and dilute 25 mL of the filtrate to 50 mL.

(2) 0.05% w/v of *cefalexin BPCRS*.

(3) 0.01% w/v of each of *cefalexin BPCRS* and *cefradine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *methanol*, 5 volumes of *acetonitrile*, 10 volumes of a 1.36% w/v solution of *potassium dihydrogen orthophosphate* and 83 volumes of *water*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to cefalexin and cefradine is at least 4.0; if necessary, adjust the *acetonitrile* content of the mobile phase.

Inject solution (2) six times. The Assay is not valid unless the relative standard deviation of the area of the principal peak is at most 1.0%.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{17}N_3O_4S$ in the tablets using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS*.

STORAGE

Cefalexin Tablets should be stored at a temperature not exceeding 30°.

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous cefalexin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

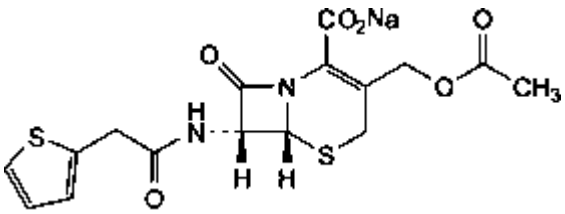
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Cefalotin Sodium

General Notices

(Ph. Eur. monograph 0987)



$C_{16}H_{15}N_2NaO_6S_2$ 418.4 *58-71-9*

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

Sodium (6*R*,7*R*)-3-[(acetyloxy)methyl]-8-oxo-7-[(thiophen-2-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, practically insoluble in anhydrous ethanol.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *cefalotin sodium CRS*.

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and its absorbance (2.2.25) at 450 nm is not greater than 0.20.

pH (2.2.3)

4.5 to 7.0 for solution S.

Specific optical rotation (2.2.7)

+ 124 to + 134 (anhydrous substance).

Dissolve 1.25 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution (a) Dissolve 75.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with *water R*.

Reference solution (a) Dissolve 75.0 mg of *cefalotin sodium CRS* in *water R* and dilute to 25.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *water R*.

Reference solution (c) Mix 1 mL of test solution (a), 1 mL of *hydrochloric acid R1* and 8 mL of *water R*. Heat at 60 °C for 12 min and cool to room temperature in iced water. Inject immediately.

Reference solution (d) Dissolve 5 mg of *cefalotin for impurity B identification CRS* in *water R* and dilute to 5 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 3 volumes of *acetonitrile for chromatography R* and 97 volumes of a 1.742 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 2.5 with *phosphoric acid R*;

— *mobile phase B*: mix 40 volumes of *acetonitrile for chromatography R* and 60 volumes of a 1.742 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 2.5 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100 → 0	0 → 100
30 - 35	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c) and (d).

Relative retention With reference to cefalotin (retention time = about 26 min): impurity C = about 0.2; impurity B = about 0.7; impurity D = about 0.88; impurity A = about 0.96.

System suitability Reference solution (c):

— *resolution*: minimum 7.0 between the peaks due to impurity D and cefalotin.

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity D*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *any other impurity*: for each impurity, not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

***N*,*N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent.

Water (*2.5.12*)

Maximum 1.5 per cent, determined on 0.500 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.13 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mix 14 volumes of *acetonitrile R* and 86 volumes of a 6.967 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 6.0 with *phosphoric acid R*.

Detection Spectrophotometer at 260 nm.

Injection 5 µL of test solution (b) and reference solution (a).

Run time 1.5 times the retention time of cefalotin (retention time = about 10 min).

Calculate the percentage content of $C_{16}H_{15}N_2NaO_6S_2$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *cefalotin sodium CRS*.

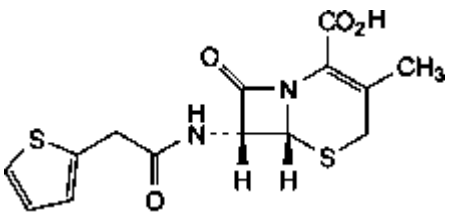
STORAGE

Protected from light, in an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

Specified impurities *B, D.*

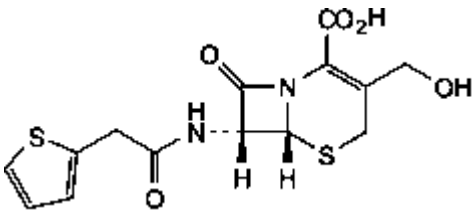
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C.*



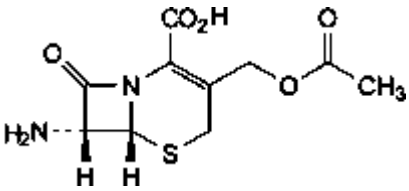
A. (6*R*,7*R*)-3-methyl-8-oxo-7-[(thiophen-2-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetoxycefalotin),

www.webofpharma.com

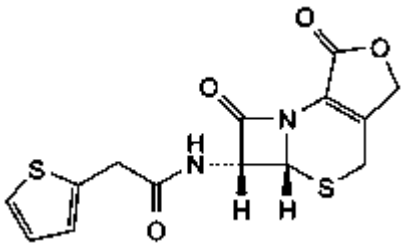
https://thuvienthuocngocanh.com/



B. (6*R*,7*R*)-3-(hydroxymethyl)-8-oxo-7-[(thiophen-2-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetylcefalotin),



C. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA),



D. (5a*R*,6*R*)-6-[(thiophen-2-ylacetyl)amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione (cefalotin lactone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

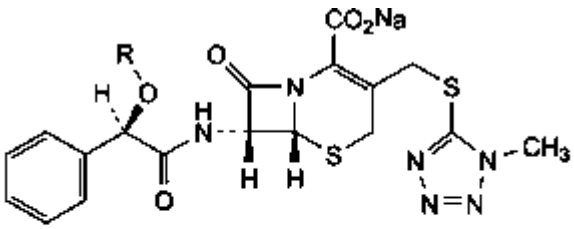
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefamandole Nafate

General Notices

(Ph. Eur. monograph 1402)



Compound	R	Molecular Formula	M_r
Cefamandole nafate	CHO	$C_{19}H_{17}N_6NaO_6S_2$	512.5
Cefamandole sodium	H	$C_{18}H_{17}N_6NaO_5S_2$	484.5

Cefamandole nafate *42540-40-9*

Cefamandole sodium *30034-03-8*

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

Mixture of sodium (6*R*,7*R*)-7-[[(2*R*)-2-(formyloxy)-2-phenylacetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate and sodium (6*R*,7*R*)-7-[[(2*R*)-2-hydroxy-2-phenylacetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (cefamandole sodium), with sodium carbonate.

Semi-synthetic product derived from a fermentation product.

Content

— *cefamandole nafate* ($C_{19}H_{17}N_6NaO_6S_2$): 93.0 per cent to 102.0 per cent (anhydrous and sodium carbonate-free substance), for the sum of the content of cefamandole nafate and cefamandole sodium expressed as cefamandole nafate;

— *cefamandole sodium* ($C_{18}H_{17}N_6NaO_5S_2$): maximum 10.0 per cent (anhydrous and sodium carbonate-free substance);

— *sodium carbonate* (Na_2CO_3): 4.8 per cent to 6.4 per cent.

CHARACTERS

www.webofpharma.com

https://thuathuocngocanh.com/

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, sparingly soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefamandole nafate CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 475 nm is not greater than 0.03.

pH

6.0 to 8.0 for solution S, measured after 30 min.

Specific optical rotation (*2.2.7*)

-35.0 to -45.0 (anhydrous and sodium carbonate-free substance).

Dissolve 1.00 g in *acetate buffer solution pH 4.7 R1* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Solvent mixture Mix 18 volumes of *acetonitrile R* and 75 volumes of a 10 per cent *V/V* solution of *triethylamine R* previously adjusted to pH 2.5 with *phosphoric acid R*.

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1 mL of the test solution to 10 mL with the solvent mixture, then heat at 60 °C for 30 min.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase:* *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *triethylamine phosphate solution*: dissolve 2.0 g of *sodium pentanesulfonate R* in 350 mL of *water R*, add 40 mL of *triethylamine R*, adjust to pH 2.5 with *phosphoric acid R* and dilute to 700 mL with *water R*;

— *mobile phase A:* mix 1 volume of the triethylamine phosphate solution and 2 volumes of *water R*;

— *mobile phase B*: mix equal volumes of the triethylamine phosphate solution, *methanol R* and *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	100	0
1 - 35	100 → 0	0 → 100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL loop injector.

Relative retention With reference to cefamandole nafate (retention time = about 24 min): cefamandole = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to cefamandole and cefamandole nafate.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (5.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

2-Ethylhexanoic acid (2.4.28)

Maximum 0.3 per cent *m/m*.

Water (2.5.12)

Maximum 2.0 per cent, determined on 0.500 g.

www.webofpharma.com

https://thuocngocanh.com/

Bacterial endotoxins (*2.6.14*)

Less than 0.15 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Cefamandole nafate

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *cefamandole nafate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1 mL of the test solution to 10 mL with the mobile phase, then heat at 60 °C for 30 min.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 25 volumes of *acetonitrile R* and 75 volumes of a 10 per cent *V/V* solution of *triethylamine R* previously adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL loop injector.

System suitability:

— *resolution*: minimum 7.0 between the 2 principal peaks in the chromatogram obtained with reference solution (b);

— *repeatability*: maximum relative standard deviation of 0.8 per cent after a series of single injections of not less than 3 freshly prepared reference solutions (a).

Calculate the percentage content of cefamandole nafate ($C_{19}H_{17}N_6NaO_6S_2$) from the sum of the contents of cefamandole nafate and cefamandole sodium expressed as cefamandole nafate, using the declared content of *cefamandole nafate CRS*.

1 mg of cefamandole sodium is equivalent to 1.0578 mg of cefamandole nafate.

Sodium carbonate

Dissolve 0.500 g in 50 mL of *water R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 5.3 mg of Na_2CO_3.

www.webofpharma.com

https://thuocngocanh.com/

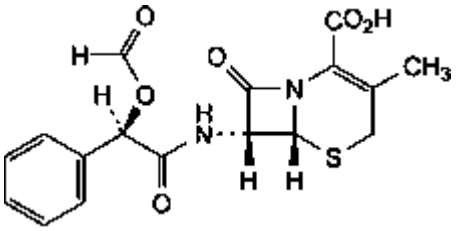
STORAGE

In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

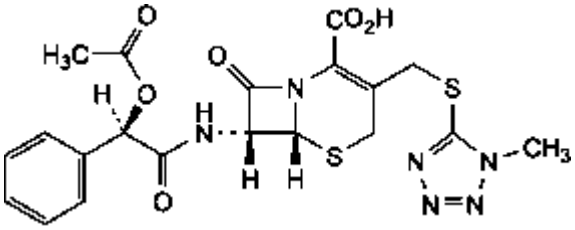
LABELLING

The label states that the substance contains sodium carbonate.

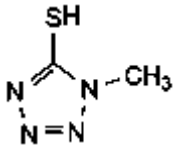
IMPURITIES



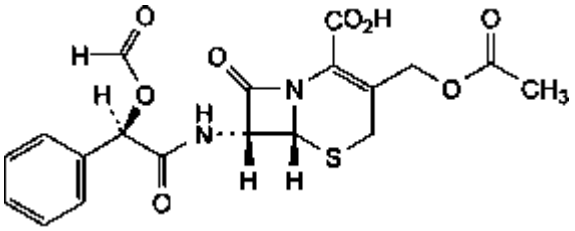
A. (6*R*,7*R*)-7-[[(2*R*)-2-(formyloxy)-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (formylmandeloyl-7-amino-desacetoxy-cephalosporanic acid),



C. (6*R*,7*R*)-7-[[(2*R*)-2-(acetyloxy)-2-phenylacetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (*O*-acetylcefamandole),



D. 1-methyl-1*H*-tetrazole-5-thiol,



E. (6*R*,7*R*)-7-[[(2*R*)-2-(formyloxy)-2-phenylacetyl]amino]-3-[(acetyloxy)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (formylmandeloyl-7-ACA).

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

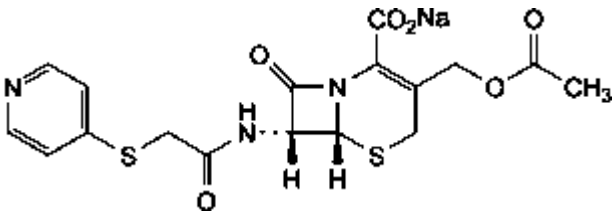
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefapirin Sodium

General Notices

(Ph. Eur. monograph 1650)



$C_{17}H_{16}N_3NaO_6S_2$ 445.5 *24356-60-3*

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

Sodium (6*R*,7*R*)-3-[(acetyloxy)methyl]-8-oxo-7-[[[(pyridin-4-yl)sulfanyl]acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow powder.

Solubility

Soluble in water, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefapirin sodium CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Appearance of solution

Dissolve 2.0 g in *water R* and dilute to 10.0 mL with the same solvent. The solution is clear (2.2.1). Dilute 5.0 mL to 10.0 mL with *water R*. The absorbance (2.2.25) of this solution at 450 nm is not greater than 0.25.

pH (2.2.3)

6.5 to 8.5.

Dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 150 to + 165 (anhydrous substance).

Dissolve 0.500 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 42 mg of the substance to be examined in the mobile phase and dilute to 200.0 mL with the mobile phase.

Reference solution (a) Dissolve 42 mg of *cefapirin sodium CRS* in the mobile phase and dilute to 200.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 20.0 mL with the mobile phase.

Reference solution (d) Mix 1 mL of the test solution, 8 mL of the mobile phase and 1 mL of *hydrochloric acid R1*. Heat at 60 °C for 10 min.

Column:

— *size*: *l* = 0.30 m, Ø = 4 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase Mix 80 mL of *dimethylformamide R*, 4.0 mL of *glacial acetic acid R* and 20 mL of a 4.5 per cent *m/m* solution of *potassium hydroxide R*. Dilute to 2 L with *water R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

www.webofpharma.com

https://thuocngocanh.com/

Run time Twice the retention time of cefapirin.

Relative retention With reference to cefapirin (retention time = about 13 min): impurity B = about 0.3; impurity C = about 0.5; impurity A = about 0.75.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to cefapirin and impurity A.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent), and not more than 1 such peak has an area greater than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent),

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.5 per cent.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.300 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.17 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{17}H_{16}N_3NaO_6S_2$.

STORAGE

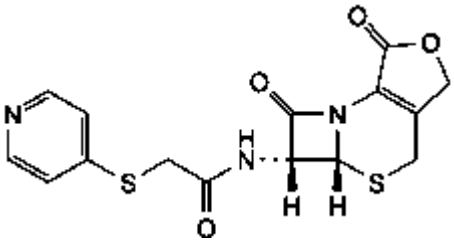
Protected from light. If the substance is sterile, store in a sterile, tamper-evident container.

www.webofpharma.com

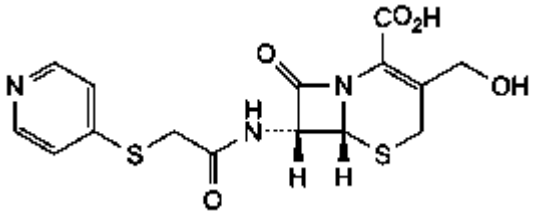
https://thuocngocanh.com/

IMPURITIES

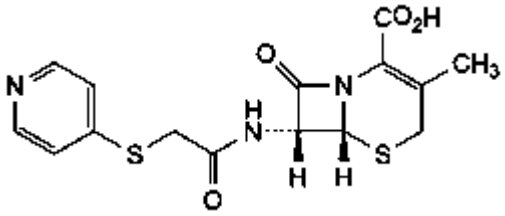
Specified impurities A, B, C.



A. (5a*R*,6*R*)-6-[[[(pyridin-4-yl)sulfanyl]acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione (deacetylcefapirin lactone),



B. (6*R*,7*R*)-3-(hydroxymethyl)-8-oxo-7-[[[(pyridin-4-yl)sulfanyl]acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetylcefapirin),



C. (6*R*,7*R*)-3-methyl-8-oxo-7-[[[(pyridin-4-yl)sulfanyl]acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetoxycefapirin).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

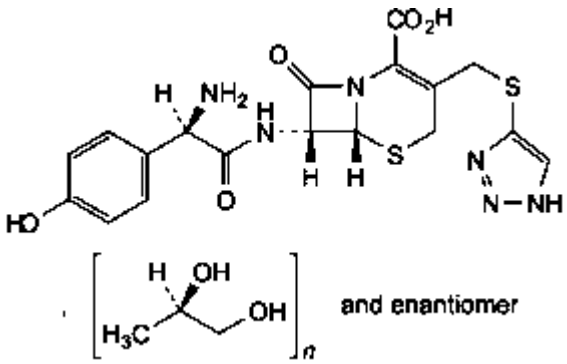
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefatrizine Propylene Glycol

General Notices

(Ph. Eur. monograph 1403)



$C_{18}H_{18}N_6O_5S_2,(C_3H_8O_2)_n$ 462.5 (base)

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

Mixture of (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-[[(1*H*-1,2,3-triazol-4-yl)sulfanyl]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid and propane-1,2-diol in molecular proportions of about 1:1.

Content

95.0 per cent to 102.0 per cent of $C_{18}H_{18}N_6O_5S_2$ (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefatrizine propylene glycol CRS*.

B. Examine the chromatograms obtained in the test for propylene glycol.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

Specific optical rotation (*2.2.7*)

+ 63 to + 69 (anhydrous substance).

Dissolve 0.400 g in *1 M hydrochloric acid* and dilute to 20.0 mL with the same acid.

Propylene glycol

Gas chromatography (*2.2.28*).

Solvent mixture *acetone R*, *water R* (20:80 *V/V*).

Internal standard solution Dissolve 1.0 g of *dimethylacetamide R* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution Introduce 0.40 g of the substance to be examined into a ground-glass-stoppered test-tube. Add 3.0 mL of the internal standard solution, 1.0 mL of the solvent mixture and 2.0 mL of *hydrochloric acid R*. Seal the test-tube and shake.

Reference solution (a) Dissolve 2.0 g of *propylene glycol R* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Introduce into a ground-glass-stoppered test-tube 1.0 mL of reference solution (a) and 1.0 mL of the internal standard solution.

Column:

— *material*: stainless steel;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (150-180 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 200 °C;

— *injection port and detector*: 250 °C.

www.webofpharma.com

https://thuocngocanh.com/

Detection Flame ionisation.

Injection 1 µL of the test solution and reference solution (b).

Limit:

— *propylene glycol*: 13.0 per cent to 18.0 per cent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 60.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 60.0 mg of *cefatrizine propylene glycol CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 30.0 mg of *cefatrizine impurity A CRS* in *buffer solution pH 7.0 R* and dilute to 100.0 mL with the same buffer solution.

Reference solution (c) Dilute 0.6 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of reference solution (b) to 100.0 mL with *buffer solution pH 7.0 R*.

Reference solution (e) To 1.0 mL of reference solution (a) add 1.0 mL of reference solution (b) and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 5 volumes of *acetonitrile R* and 95 volumes of a 2.72 g/L solution of *potassium dihydrogen phosphate R* in *water R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 µL of the test solution and reference solutions (c), (d) and (e).

Run time At least twice the retention time of cefatrizine.

System suitability Reference solution (e):

— *resolution*: minimum 5.0 between the peaks due to cefatrizine and impurity A.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent);

— *sum of impurities other than A*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.1 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.03 per cent).

Water (2.5.12)

Maximum 1.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

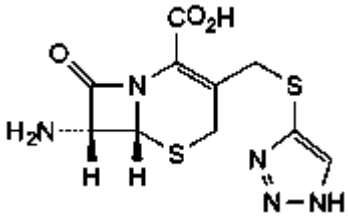
System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{18}H_{18}N_6O_5S_2$ from the declared content of $C_{18}H_{18}N_6O_5S_2$ in *cefatrizine propylene glycol CRS*.

IMPURITIES

Specified impurities *A.*



A. (6*R*,7*R*)-7-amino-8-oxo-3-[[(1*H*-1,2,3-triazol-4-yl)sulfanyl]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA triazole).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefazolin Injection

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefazolin Injection is a sterile solution of Cefazolin Sodium in Water for Injections. It is prepared by dissolving Cefazolin Sodium for Injection in the requisite amount of Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Cefazolin Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

CEFAZOLIN SODIUM FOR INJECTION

DEFINITION

Cefazolin Sodium for Injection is a sterile material consisting of Cefazolin Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of cefazolin, $C_{14}H_{14}N_8O_4S_3$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of a sealed container in sufficient of a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0* to produce a solution containing the equivalent of 0.4% w/v of cefazolin.

(2) 0.4% w/v of *cefazolin sodium BPCRS* in a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0*.

(3) 0.4% w/v each of *cefazolin sodium BPCRS* and *cefoxitin sodium BPCRS* in a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silanised silica gel* HF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

15 volumes of *acetonitrile* and 85 volumes of a 15% w/v solution of *ammonium acetate*, previously adjusted to pH 6.2 with 5M *acetic acid*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots.

B. Yield reaction A characteristic *of sodium salts*, Appendix VI.

TESTS

Acidity

pH of a solution containing the equivalent of 10.0% w/v of cefazolin, 4.0 to 6.0, Appendix V L.

Clarity of solution

A solution containing the equivalent of 10.0% w/v of cefazolin in *carbon dioxide-free water* is *clear,* Appendix IV A. The *absorbance* of the solution measured at 430 nm is not greater than 0.15, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve the contents of a sealed container in sufficient mobile phase A to produce a solution containing the equivalent of 0.25% w/v of cefazolin.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) Dissolve 20 mg of *cefazolin sodium BPCRS* in 10 mL of a 0.2% w/v solution of *sodium hydroxide*, allow to stand for 15 to 30 minutes and dilute 1 volume to 20 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil 120-3 C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 5 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

Mobile phase A A solution containing 1.454% w/v of *disodium hydrogen orthophosphate* and 0.353% w/v of *potassium dihydrogen orthophosphate*.

Mobile phase B *acetonitrile for chromatography*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	98	2	isocratic
2-4	98 → 85	2 → 15	linear gradient
4-10	85 → 60	15 → 40	linear gradient
10-11.5	60 → 35	40 → 65	linear gradient
11.5-12	35	65	isocratic
12-15	35 → 98	65 → 2	linear gradient
15-21	98	2	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefazolin and the peak with a retention time relative to cefazolin of about 1.1 (cefazolin impurity L) is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Water

Not more than 6.0% w/w, Appendix IX C, Method I. Use 0.3 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of cefazolin per mL (solution A). The endotoxin limit concentration of solution A is 1.5 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a quantity of the mixed contents of the 10 containers to produce a solution containing the equivalent of 0.1% w/v of cefazolin.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.1% w/v of *cefazolin sodium BPCRS*.

(3) 0.005% w/v of *cefuroxime sodium BPCRS* and 0.01% w/v of *cefazolin sodium BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of 10 volumes of *acetonitrile* and 90 volumes of a solution containing 0.277% w/v of *disodium hydrogen orthophosphate* and 0.186% w/v of *citric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to cefazolin and cefuroxime is at least 2.0. If necessary, adjust the concentration of *acetonitrile* in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{14}N_8O_4S_3$ in a container of average content weight from the declared content of $C_{14}H_{14}N_8O_4S_3$ in *cefazolin sodium BPCRS*.

STORAGE

The sealed container should be protected from light and stored at a temperature not exceeding 30°.

LABELLING

The label on the sealed container states the quantity of Cefazolin Sodium contained in it in terms of the equivalent amount of cefazolin.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

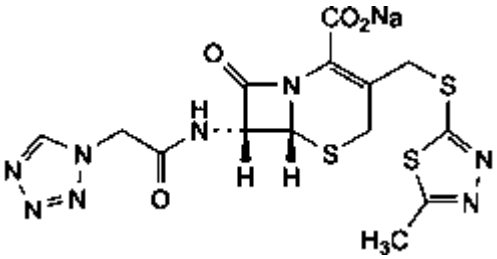
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefazolin Sodium

General Notices

(Ph. Eur. monograph 0988)



$C_{14}H_{13}N_8NaO_4S_3$ 476.5 *27164-46-1*

Action and use

Cephalosporin antibacterial.

Preparation

Cefazolin Injection

Ph Eur

DEFINITION

Sodium (6*R*,7*R*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, very hygroscopic.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 0.150 g in 5 mL of water R, add 0.5 mL of dilute acetic acid R, swirl and allow to stand for 10 min in iced water. Filter the precipitate and rinse with 1-2 mL of water R. Dissolve in a mixture of 1 volume of water R and 9 volumes of acetone R. Evaporate the solvent almost to dryness, then dry in an oven at 60 °C for 30 min.

Comparison cefazolin CRS.

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in carbon dioxide-free water R and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and its absorbance (2.2.25) at 430 nm is not greater than 0.15.

pH (2.2.3)

4.0 to 6.0 for solution S.

Specific optical rotation (2.2.7)

-24 to -15 (anhydrous substance).

Dissolve 1.25 g in water R and dilute to 25.0 mL with the same solvent.

Absorbance (2.2.25)

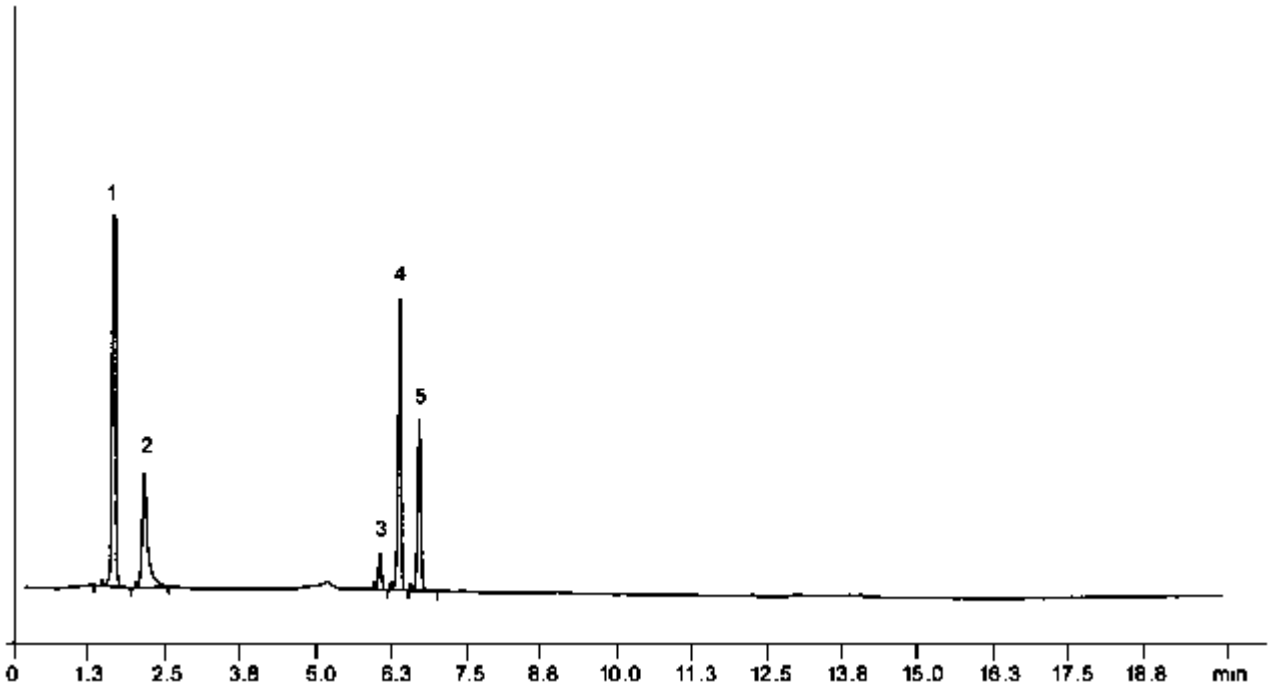
Dissolve 0.100 g in water R and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with sodium hydrogen carbonate solution R. Examined between 220 nm and 350 nm, the solution shows an absorption maximum at 272 nm. The specific absorbance at the maximum is 260 to 300 (anhydrous substance).

Related substances

Liquid chromatography (2.2.29).

www.webofpharma.com

https://thuocngocanh.com/



1. impurity J 2. impurity E 3. unknown structure 4. cefazolin 5. impurity L

Figure 0988.-1. – *Chromatogram for the test for related substances of cefazolin sodium: reference solution (b) (in situ degradation)*

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (b) Dissolve 20 mg of the substance to be examined in 10 mL of a 2 g/L solution of *sodium hydroxide R*. Allow to stand for 15-30 min. Dilute 1.0 mL of the solution to 20 mL with mobile phase A.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: solution containing 14.54 g/L of *disodium hydrogen phosphate dodecahydrate R* and 3.53 g/L of *potassium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile R*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	98	2
2 - 4	98 → 85	2 → 15
4 - 10	85 → 60	15 → 40
10 - 11.5	60 → 35	40 → 65
11.5 - 12	35	65
12 - 15	35 → 98	65 → 2
15 - 21	98	2

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 5 µL.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to cefazolin and impurity L (see Figure 0988.-1).

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *total*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.5 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

Water (*2.5.12*)

Maximum 6.0 per cent, determined on 0.300 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.15 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *cefazolin CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *cefuroxime sodium CRS* in 10.0 mL of reference solution (a) and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 10 volumes of *acetonitrile R* and 90 volumes of a solution containing 2.77 g/L of *disodium hydrogen phosphate dodecahydrate R* and 1.86 g/L of *citric acid monohydrate R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 20 µL.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to cefazolin and cefuroxime in the chromatogram obtained with reference solution (b);

— *symmetry factor*: 0.8 to 3.0 for the peak due to cefazolin in the chromatogram obtained with reference solution (a).

Calculate the percentage content of $C_{14}H_{13}N_8NaO_4S_3$ taking into account the assigned content of *cefazolin CRS* and a conversion factor of 1.048.

STORAGE

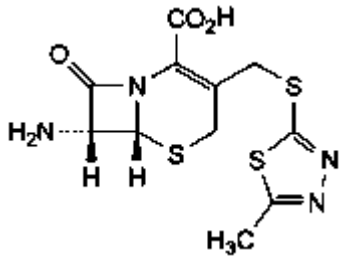
In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

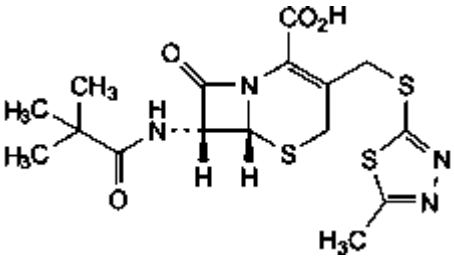
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, G, H, I, J, K, L.*

www.webofpharma.com

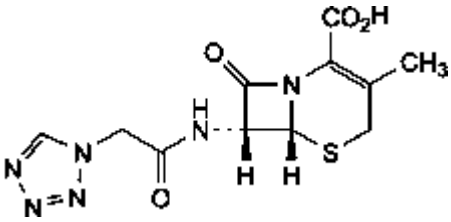
https://thuocngocanh.com/



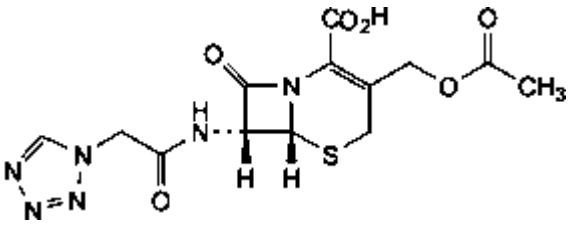
A. (6*R*,7*R*)-7-amino-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



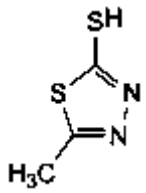
B. (6*R*,7*R*)-7-[(2,2-dimethylpropanoyl)amino]-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



C. (6*R*,7*R*)-3-methyl-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



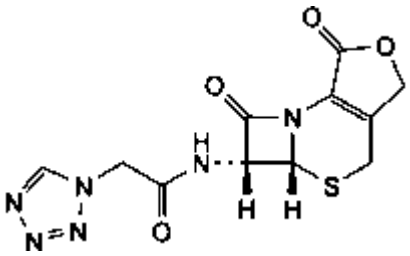
D. (6*R*,7*R*)-3-[(acetyloxy)methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



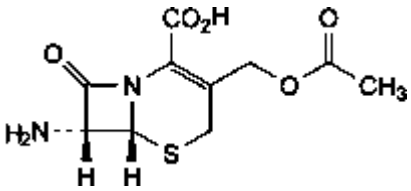
E. 5-methyl-1,3,4-thiadiazol-2-thiol (MMTD),

www.webofpharma.com

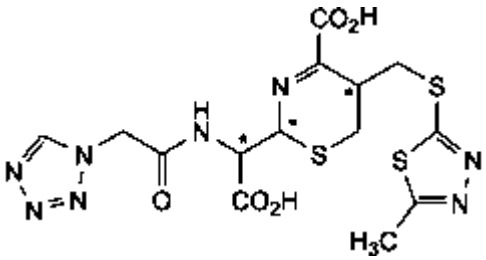
https://thuocngocanh.com/



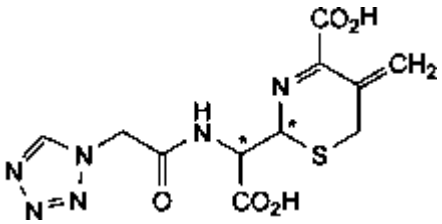
G. (5a*R*,6*R*)-6-[(1*H*-tetrazol-1-ylacetyl)amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione,



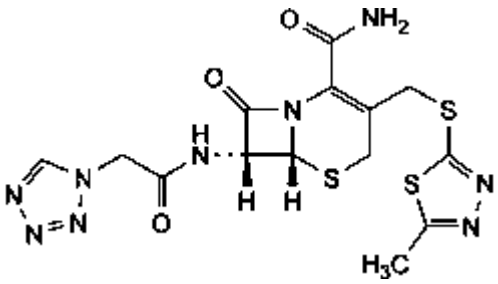
H. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA),



I. 2-[carboxy[(1*H*-tetrazol-1-ylacetyl)amino]methyl]-5-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-5,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid (cefazoloic acid),



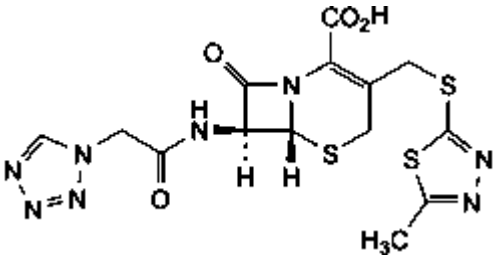
J. 2-[carboxy[(1*H*-tetrazol-1-ylacetyl)amino]methyl]-5-methylidene-5,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid,



K. (6*R*,7*R*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxamide (cefazolinamide),

www.webofpharma.com

https://thuvienthuocngocanh.com/



L. (6*R*,7*S*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

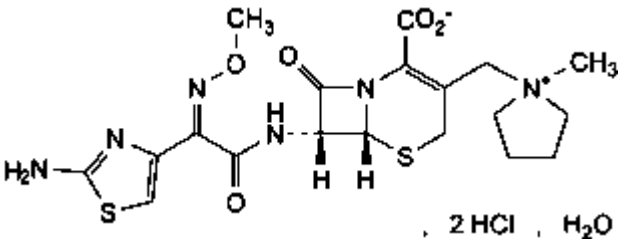
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefepime Hydrochloride Monohydrate

General Notices

(Cefepime Dihydrochloride Monohydrate, Ph. Eur. monograph 2126)



$C_{19}H_{26}Cl_2N_6O_5S_2,H_2O$ 571.5 *123171-59-5*

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

(6*R*,7*R*)-7-[[(2*Z*)-(2-Aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate dihydrochloride monohydrate. Semi-synthetic product derived from a fermentation product.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefepime dihydrochloride monohydrate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_3 (2.2.2, Method II).

Dissolve 2.0 g in water R and dilute to 20 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 40 to + 45 (anhydrous substance).

Dissolve 0.250 g in water R and dilute to 25.0 mL with the same solvent.

Impurity G

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.100 g of the substance to be examined in 0.01 M nitric acid and dilute to 10.0 mL with the same acid.

Reference solution (a) Dilute 0.250 g of N-methylpyrrolidine R (impurity G) to 100.0 mL with water R. Dilute 2.0 mL of this solution to 100.0 mL with 0.01 M nitric acid.

Reference solution (b) Dilute 0.250 g of pyrrolidine R to 100 mL with 0.01 M nitric acid. Dilute 2 mL of the solution to 100 mL with 0.01 M nitric acid. Mix 5 mL of this solution with 5 mL of reference solution (a).

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: strong cation-exchange resin R (5 µm).

Mobile phase Mix 1 volume of acetonitrile R and 100 volumes of 0.01 M nitric acid; filter through a 0.2 µm filter.

Flow rate 1 mL/min.

Detection Conductivity detector.

Injection 100 µL.

Run time 1.1 times the retention time of cefepime.

Retention time Cefepime = about 50 min, eluting as a broadened peak.

System suitability:

— symmetry factor: maximum 2.5 for the peak due to impurity G in the chromatogram obtained with reference solution (a);

www.webofpharma.com

https://thuocngocanh.com/

— *repeatability*: maximum relative standard deviation of 5.0 per cent after 6 injections of reference solution (a);

— *peak-to-valley ratio*: minimum 3 between the peaks due to pyrrolidine and impurity G in the chromatogram obtained with reference solution (b).

Calculate the percentage content of impurity G in the test solution using reference solution (a).

Limit:

— *impurity G*: maximum 0.5 per cent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or keep refrigerated at 4-8 °C for not more than 12 h.*

Test solution Dissolve 70.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A. Sonicate for 30 s and stir for about 5 min.

Reference solution (a) Dissolve 70.0 mg of *cefepime dihydrochloride monohydrate CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A. Sonicate for 30 s and stir for about 5 min.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with mobile phase A. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase A.

Reference solution (c) Dissolve 7 mg of *cefepime dihydrochloride monohydrate for system suitability CRS* (containing impurities A, B and F) in mobile phase A and dilute to 5 mL with mobile phase A.

Reference solution (d) Dissolve 2 mg of *cefepime impurity E CRS* in mobile phase A and dilute to 25.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 10 volumes of *acetonitrile R* and 90 volumes of a 0.68 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with a 0.5 M potassium hydroxide solution prepared from *potassium hydroxide R*;

— *mobile phase B*: mix equal volumes of *acetonitrile R* and a 0.68 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with a 0.5 M potassium hydroxide solution prepared from *potassium hydroxide R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
10 - 30	100 → 50	0 → 50
30 - 35	50	50
35 - 36	50 → 100	50 → 0
36 - 45	100	0

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *cefepime dihydrochloride monohydrate for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and F; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity E.

Relative retention With reference to cefepime (retention time = about 7 min): impurity E = about 0.4; impurity F = about 0.8; impurity A = about 2.5; impurity B = about 4.1.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity F and cefepime.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.4; impurity B = 1.4; impurity E = 1.8;

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities B, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity E*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

www.webofpharma.com

https://thuvienthuocngocanh.com/

Water (*2.5.12*)

3.0 per cent to 4.5 per cent, determined on 0.400 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.04 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase A.

Injection Test solution and reference solution (a).

Run time 1.4 times the retention time of cefepime.

Calculate the percentage content of $C_{19}H_{26}Cl_2N_6O_5S_2$ from the declared content of *cefepime dihydrochloride monohydrate CRS*.

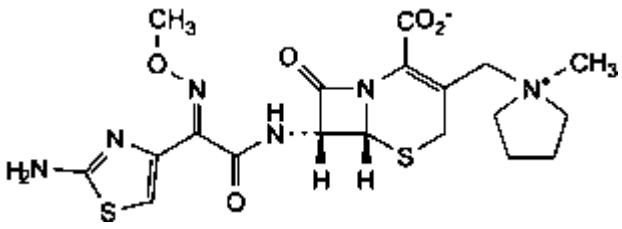
STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Specified impurities *A, B, E, F, G.*

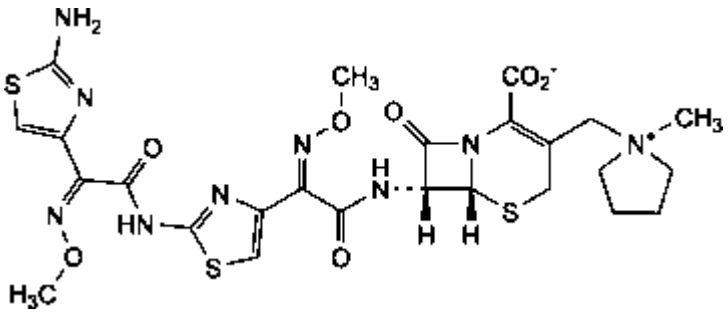
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D.*



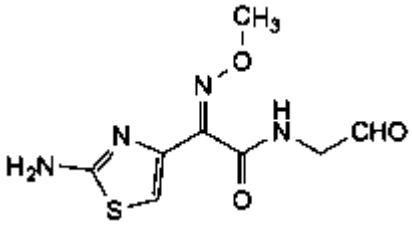
A. (6*R*,7*R*)-7-[[(2*E*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (*anti*-cefepime),

www.webofpharma.com

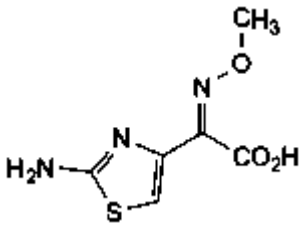
https://thuocngocanh.com/



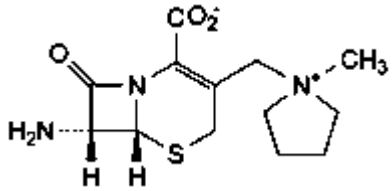
B. (6*R*,7*R*)-7-[[(2*Z*)-[2-[[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]thiazol-4-yl](methoxyimino)acetyl]amino]-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



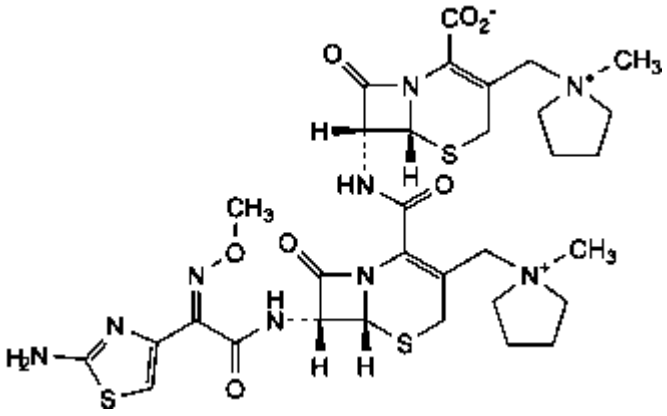
C. (2*Z*)-2-(2-aminothiazol-4-yl)-*N*-(formylmethyl)-2-(methoxyimino)acetamide,



D. (2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetic acid,



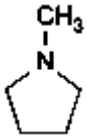
E. (6*R*,7*R*)-7-amino-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



www.webofpharma.com

https://thuocngocanh.com/

F. (6*R*,7*R*)-7-[[[(6*R*,7*R*)-7-[[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-yl]carbonyl]amino]-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



G. 1-methylpyrrolidine (*N*-methylpyrrolidine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

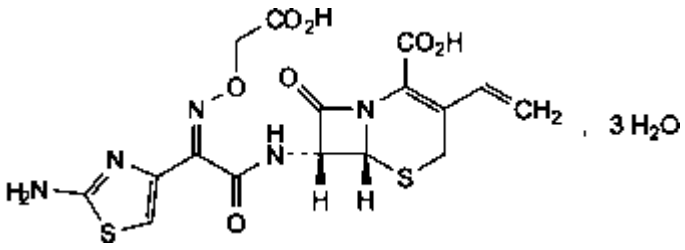
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefixime

General Notices

(Ph. Eur. monograph 1188)



$C_{16}H_{15}N_5O_7S_2,3H_2O$ 507.5

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

(6*R*,7*R*)-7-[[(*Z*)-2-(2-Aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid trihydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder.

Solubility

Slightly soluble in water, soluble in methanol, sparingly soluble in anhydrous ethanol, practically insoluble in ethyl acetate.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *cefixime CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

pH (2.2.3)

2.6 to 4.1.

Suspend 0.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *cefixime CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) In order to prepare impurity D *in situ*, dissolve 10 mg of *cefixime CRS* in 10 mL of *water R*, heat on a water-bath for 45 min and cool. Inject immediately.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

— *Mobile phase*: mix 250 volumes of *acetonitrile R* and 750 volumes of a tetrabutylammonium hydroxide solution prepared as follows: dissolve 8.2 g of *tetrabutylammonium hydroxide R* in *water for chromatography R* and dilute to 800 mL with the same solvent; adjust to pH 6.5 with *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Autosampler Set at 4 °C.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time 3 times the retention time of cefixime.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to cefixime and impurity D; if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

— *any impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Ethanol (2.4.24)

Head-space gas chromatography (2.2.28): use the standard additions method.

Sample solution Dissolve 0.250 g of the substance to be examined in *dimethylformamide R* and dilute to 25.0 mL with the same solvent.

Limit:

— *ethanol*: maximum 1.0 per cent.

Water (2.5.12)

9.0 per cent to 12.0 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: maximum 3.0 for the peak due to cefixime;

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of $C_{16}H_{15}N_5O_7S_2$ taking into account the assigned content of *cefixime CRS*.

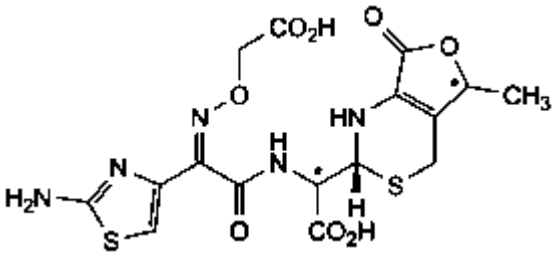
STORAGE

In an airtight container, protected from light.

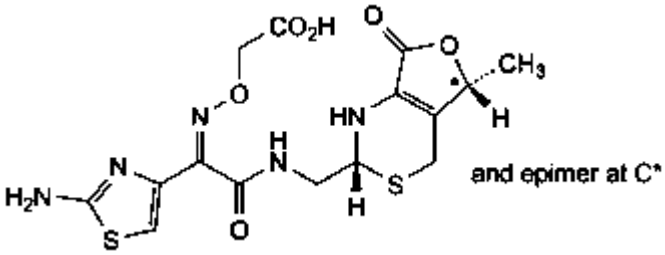
www.webofpharma.com

https://thuocngocanh.com/

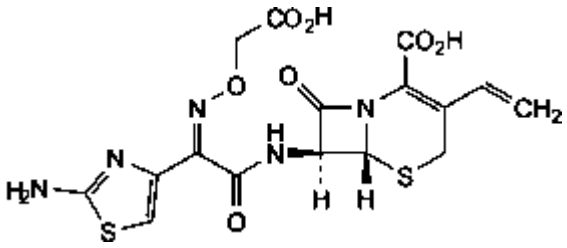
IMPURITIES



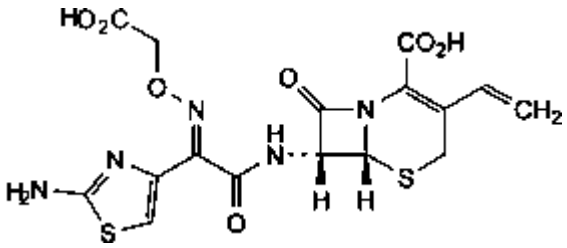
A. 2-[[(*Z*)-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-2-[(2*R*)-5-methyl-7-oxo-1,2,5,7-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-yl]acetic acid,



B. 2-[[[(*Z*)-1-(2-aminothiazol-4-yl)-2-[[[(2*R*,5*RS*)-5-methyl-7-oxo-1,2,5,7-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-yl]methyl]amino]-2-oxoethylidene]amino]oxy]acetic acid,



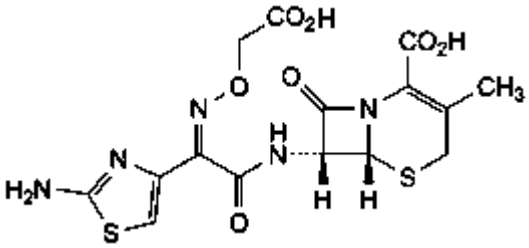
C. (6*R*,7*S*)-7-[[(*Z*)-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefixime 7-epimer),



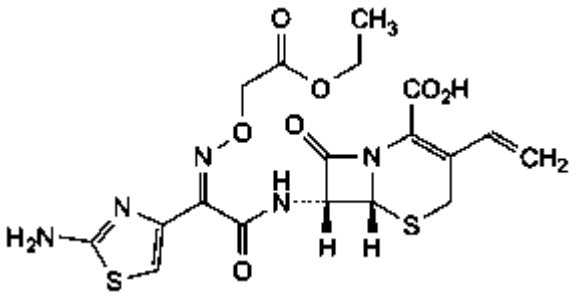
D. (6*R*,7*R*)-7-[[(*E*)-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefixime (*E*)-isomer),

www.webofpharma.com

https://thuocngocanh.com/



E. (6*R*,7*R*)-7-[[(*Z*)-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



F. (6*R*,7*R*)-7-[[(*Z*)-2-(2-aminothiazol-4-yl)-2-[(2-ethoxy-2-oxoethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

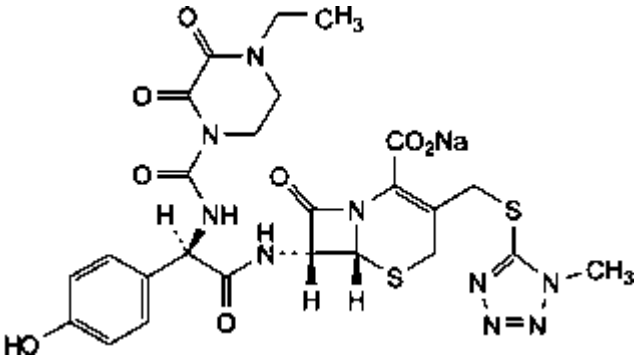
https://thuathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefoperazone Sodium

General Notices

(Ph. Eur. monograph 1404)



$C_{25}H_{26}N_9NaO_8S_2$ 668 *62893-20-3*

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

Sodium (6*R*,7*R*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow, hygroscopic powder.

Solubility

Freely soluble in water, soluble in methanol, slightly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

If crystalline, it shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve the substance to be examined in *methanol R* and evaporate to dryness; examine the residue.

Comparison *Ph. Eur. reference spectrum of cefoperazone sodium*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (a) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. It gives reaction (a) of sodium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 430 nm is not greater than 0.15.

Dissolve 2.5 g in *water R* and dilute to 25.0 mL with the same solvent.

pH (2.2.3)

4.5 to 6.5.

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 250.0 mL with the mobile phase.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *cefoperazone dihydrate CRS* in the mobile phase and dilute to 250.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 884 volumes of *water R*, 110 volumes of *acetonitrile R*, 3.5 volumes of a 60 g/L solution of *acetic acid R* and 2.5 volumes of a triethylammonium acetate solution prepared as follows: dilute 14 mL of *triethylamine R* and 5.7 mL of *glacial acetic acid R* to 100 mL with *water R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (b) and reference solutions (a) and (b).

Run time 2.5 times the retention time of cefoperazone.

Retention time Cefoperazone = about 15 min.

System suitability Reference solution (a):

— *number of theoretical plates*: minimum 5000, calculated for the principal peak; if necessary, adjust the content of *acetonitrile R* in the mobile phase;

— *symmetry factor*: maximum 1.6 for the principal peak; if necessary, adjust the content of *acetonitrile R* in the mobile phase.

Limits:

— *any impurity*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *total*: not more than 4.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (4.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Acetone (*2.4.24, System B*)

Maximum 2.0 per cent.

Sample solution Dissolve 0.500 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Solvent solution Dissolve 0.350 g of *acetone R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *water R*.

Prepare each of 4 injection vials as shown in the table below:

Vial No.	Sample solution (mL)	Solvent solution (mL)	*Water R* (mL)
1	1.0	0	4.0
2	1.0	1.0	3.0
3	1.0	2.0	2.0

www.webofpharma.com

https://thuathuocngocanh.com/

Vial No.	Sample solution (mL)	Solvent solution (mL)	*Water R* (mL)
4	1.0	3.0	1.0

Static head-space conditions that may be used:

— *equilibration time*: 15 min;

— *transfer-line temperature*: 110 °C.

Temperature:

— *Column*: 40 °C for 10 min.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.200 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.20 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of cefoperazone sodium by multiplying the percentage content of cefoperazone by 1.034.

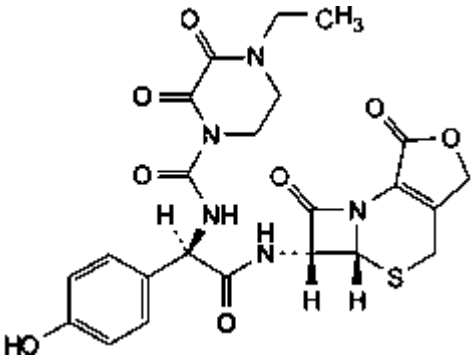
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

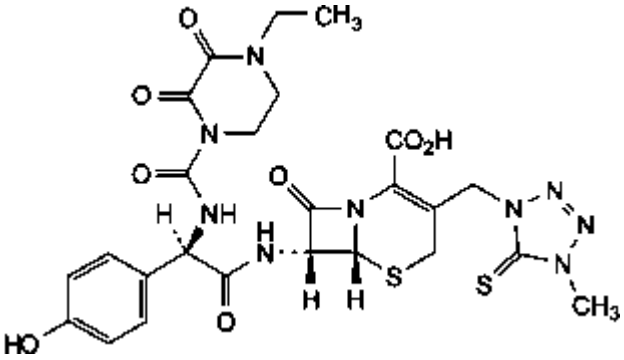
IMPURITIES

www.webofpharma.com

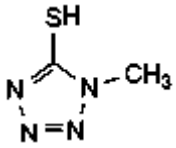
https://thuocngocanh.com/



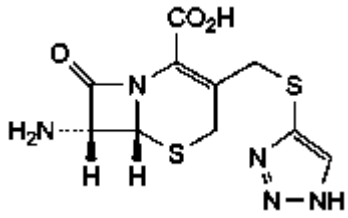
A. (5a*R*,6*R*)-6-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione,



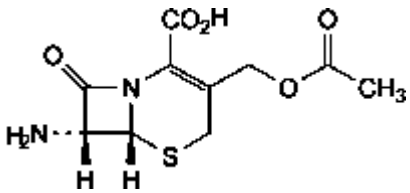
B. (6*R*,7*R*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[(4-methyl-5-thioxo-4,5-dihydro-1*H*-tetrazol-1-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



C. 1-methyl-1*H*-tetrazole-5-thiol,



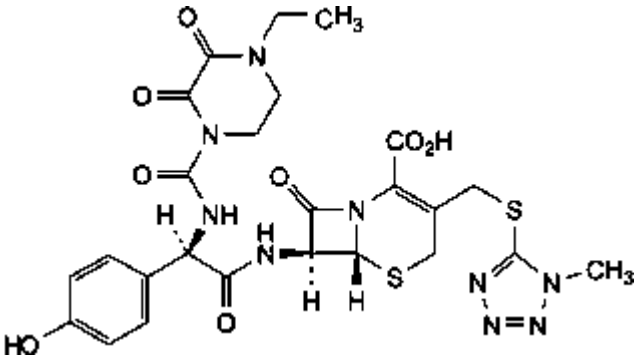
D. (6*R*,7*R*)-7-amino-8-oxo-3-[(1*H*-1,2,3-triazol-4-ylsulfanyl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-TACA),



E. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA),

www.webofpharma.com

https://thuocngocanh.com/



F. (6*R*,7*S*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazine-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefotaxime Injection

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefotaxime Injection is a sterile solution of Cefotaxime Sodium in Water for Injections. It is prepared by dissolving Cefotaxime Sodium for Injection in the requisite amount of Water for Injections before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Cefotaxime Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

CEFOTAXIME SODIUM FOR INJECTION

DEFINITION

Cefotaxime Sodium for Injection is a sterile material consisting of Cefotaxime Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of cefotaxime, $C_{16}H_{17}N_5O_7S_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of cefotaxime sodium *(RS 044)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of a sealed container in sufficient of a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0* (solution A) to produce a solution containing the equivalent of 0.4% w/v of cefotaxime.

(2) 0.4% w/v of *cefotaxime sodium EPCRS* in solution A.

(3) 0.4% w/v of each of *cefotaxime sodium EPCRS* and *cefoxitin sodium BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use as the coating *silanised silica gel* HF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

15 volumes of *acetone* and 85 volumes of a 15.4% w/v solution of *ammonium acetate*, previously adjusted to pH 6.2 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. Yields reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity

pH of a solution containing the equivalent of 10.0% w/v of cefotaxime, 4.5 to 6.5, Appendix V L.

Clarity and colour of solution

A solution containing the equivalent of 10.0% w/v of cefotaxime in *carbon dioxide-free water* is *clear*, Appendix IV A. The *absorbance* of the solution at 430 nm is not greater than 0.60, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions.

(1) Dissolve a quantity of the contents of a sealed container in sufficient of the mobile phase to produce a solution containing the equivalent of 0.1% w/v of cefotaxime.

(2) 0.001% w/v of *cefotaxime acid EPCRS* in the mobile phase.

(3) Dilute 1 mL of solution (1) to 10 mL with the mobile phase. To 4 mL of this solution add 1 mL of 2M *hydrochloric acid*, heat the solution at 40° for 2 hours, add 5 mL of *phosphate buffer pH 6.6* and 1 mL of 2M *sodium hydroxide* and mix.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 µm ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 235 nm.

(f) Inject 10 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for at least 8 times the retention time of cefotaxime.

MOBILE PHASE

Dissolve 3.5 g of *potassium dihydrogen orthophosphate* and 11.6 g of *disodium hydrogen orthophosphate* in 1000 mL of *water* at pH 7.0 and add 375 mL of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of cefotaxime is about 6 minutes. If necessary, use another stationary phase or adjust the concentration of *methanol* in the mobile phase.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), cefotaxime is eluted as the second of the principal peaks and the *resolution factor* between the two principal peaks is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all the *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4%).

Ethanol

Not more than 1.0% w/v, Appendix VIII L, System A.

Water

Not more than 3.0% w/v, Appendix IX C. Use 0.300 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of cefotaxime per mL (solution A). The endotoxin limit concentration of solution A is 0.5 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions.

(1) Dissolve a quantity of the mixed contents of the 10 containers in sufficient of the mobile phase to produce a solution containing the equivalent of 0.01% w/v of cefotaxime.

(2) 0.01% w/v of *cefotaxime acid EPCRS* in the mobile phase.

www.webofpharma.com

https://thuathuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 µm ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Dissolve 3.5 g of *potassium dihydrogen orthophosphate* and 11.6 g of *disodium hydrogen orthophosphate* in 1000 mL of *water* at pH 7.0 and add 375 mL of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is less than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{17}N_5O_7S_2$ in a container of average content weight from the declared content of $C_{16}H_{17}N_5O_7S_2$ in *cefotaxime acid EPCRS*.

STORAGE

The sealed container should be protected from light.

LABELLING

The label of the sealed container states the quantity of Cefotaxime Sodium contained in it in terms of the equivalent amount of cefotaxime.

© Crown Copyright 2022

www.webofpharma.com

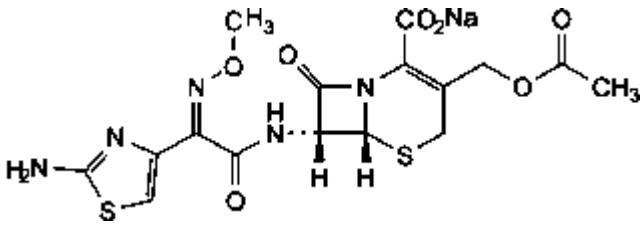
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefotaxime Sodium

General Notices

(Ph. Eur. monograph 0989)



$C_{16}H_{16}N_5NaO_7S_2$ 477.4 *64485-93-4*

Action and use

Cephalosporin antibacterial.

Preparation

Cefotaxime Injection

Ph Eur

DEFINITION

Sodium (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow powder, hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in methanol.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *cefotaxime sodium CRS*.

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1). Add 1 mL of *glacial acetic acid R* to 10 mL of solution S. The solution, examined immediately, is clear.

pH (2.2.3)

4.5 to 6.5 for solution S.

Specific optical rotation (2.2.7)

+ 58.0 to + 64.0 (anhydrous substance).

Dissolve 0.100 g in *water R* and dilute to 10.0 mL with the same solvent.

Absorbance (2.2.25)

Maximum 0.40 at 430 nm for solution S.

Specific absorbance (2.2.25)

360 to 390, determined at the absorption maximum at 235 nm (anhydrous substance).

Dissolve 20.0 mg in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solution A Mobile phase B, mobile phase A (14:86 *V/V*).

Test solution Dissolve 40.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with the same solution.

Reference solution (a) Dissolve 8.0 mg of *cefotaxime acid CRS* in solution A and dilute to 10.0 mL with the same solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with solution A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Add 1.0 mL of *dilute hydrochloric acid R* to 4.0 mL of the test solution. Heat the solution at 40 °C for 2 h. Add 5.0 mL of *buffer solution pH 6.6 R* and 1.0 mL of *dilute sodium hydroxide solution R*.

Reference solution (d) Dissolve 4 mg of *cefotaxime for peak identification CRS* (containing impurities A, B, C, E and F) in 5 mL of solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 7.1 g/L solution of *disodium hydrogen phosphate dodecahydrate R* adjusted to pH 6.25 using *phosphoric acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	86	14
7 - 9	86 → 82	14 → 18
9 - 16	82	18
16 - 45	82 → 60	18 → 40
45 - 50	60	40
50 - 55	60 → 86	40 → 14
55 - 60	86	14

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *cefotaxime for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, E and F.

Relative retention With reference to cefotaxime (retention time = about 13 min): impurity B = about 0.3; impurity A = about 0.5; impurity E = about 0.6; impurity C = about 1.9; impurity D = about 2.3; impurity F = about 2.4; impurity G = about 3.1.

System suitability Reference solution (c):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 3.5 between the peaks due to impurity E and cefotaxime;

— *symmetry factor*: maximum 2.0 for the peak due to cefotaxime.

Limits:

— *impurities A, B, C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Ethanol (*2.4.24, System A*)

Maximum 1.0 per cent.

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.5 per cent *m/m*.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.300 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.05 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{16}H_{16}N_5NaO_7S_2$ by multiplying the percentage content of cefotaxime by 1.048.

STORAGE

In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

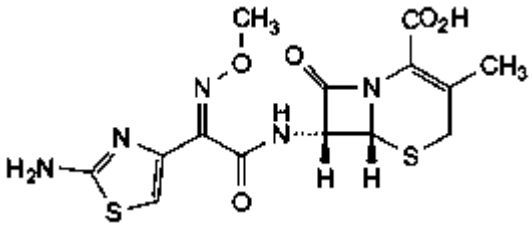
www.webofpharma.com

https://thuvienthuocngocanh.com/

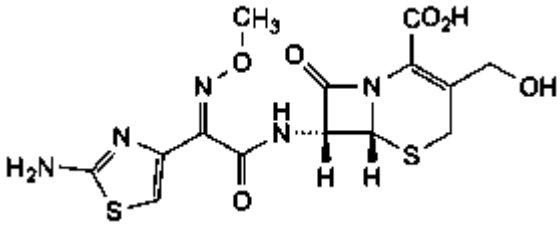
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

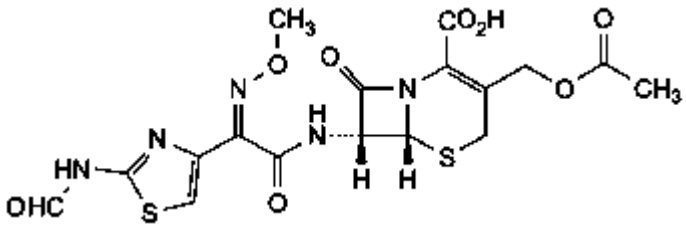
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G.*



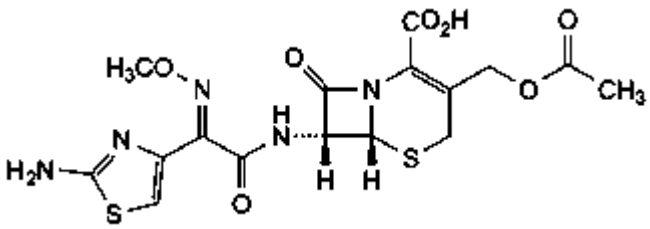
A. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetoxycefotaxime),



B. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetylcefotaxime),



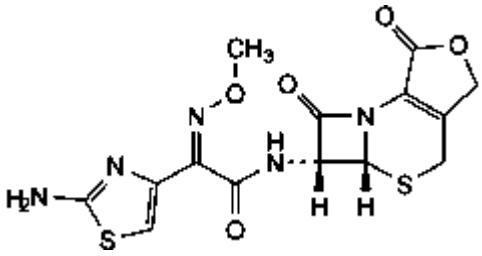
C. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*Z*)-2-[2-(formylamino)thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (*N*-formylcefotaxime),



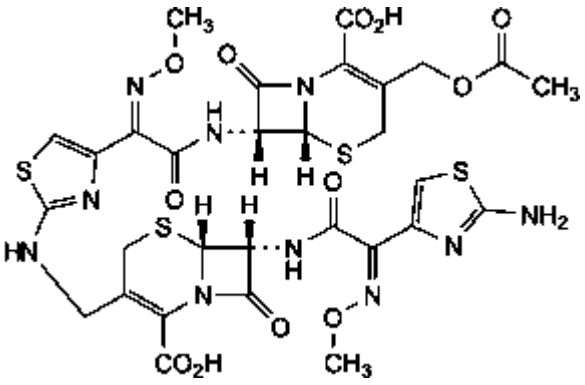
www.webofpharma.com

https://thuocngocanh.com/

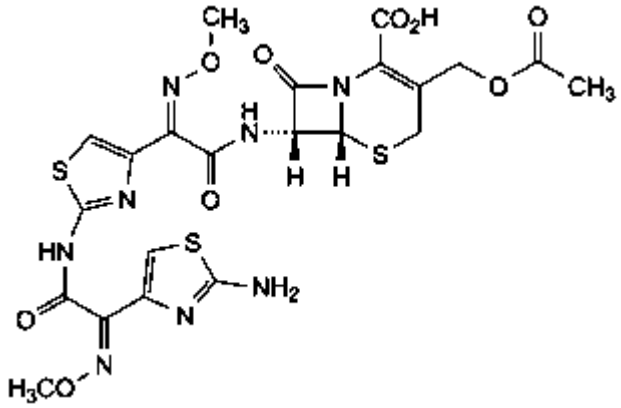
D. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*E*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid ((*E*)-cefotaxime),



E. (5a*R*,6*R*)-6-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione (deacetylcefotaxime lactone),



F. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*Z*)-2-[2-[[[(6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-yl]methyl]amino]thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefotaxime dimer),



G. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*Z*)-2-[2-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (ATA cefotaxime).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefoxitin Injection

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefoxitin Injection is a sterile solution of Cefoxitin Sodium in Water for Injections. It is prepared by dissolving Cefoxitin Sodium for Injection in the requisite amount of Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Cefoxitin Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

CEFOXITIN SODIUM FOR INJECTION

DEFINITION

Cefoxitin Sodium for Injection is a sterile material consisting of Cefoxitin Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of cefoxitin, $C_{16}H_{17}N_3O_7S_2$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of cefoxitin sodium *(RS 045)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of a sealed container in sufficient of a mixture of equal volumes of *methanol* and *0.067*M *mixed phosphate buffer pH 7.0* (solution A) to produce a solution containing the equivalent of 0.4% w/v of cefoxitin.

(2) 0.4% w/v of *cefoxitin sodium BPCRS* in solution A.

(3) 0.4% w/v of each of *cefoxitin sodium BPCRS* and *cefazolin sodium BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use as the coating *silanised* *silica gel* HF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *tetrahydrofuran* and 90 volumes of a 15.4% w/v solution of *ammonium acetate* previously adjusted to pH 6.2 with 5M *acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. Yield reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 1.0% w/v of cefoxitin, 4.2 to 7.0, Appendix V L.

Clarity and colour of solution

A solution containing the equivalent of 10.0% w/v of cefoxitin in *carbon dioxide-free water* is *clear*, Appendix IV A, and not more intensely coloured than intensity *5* of the range of reference solutions of the most appropriate colour, Appendix IV B, Method II.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use. Dilute 20 mL of a 3.48% w/v solution of *dipotassium hydrogen orthophosphate*, adjusted to pH 6.8 with *orthophosphoric acid*, to 1000 mL with *water* (solution B).

(1) Dissolve a quantity of the contents of a sealed container in sufficient of solution B to produce a solution containing the equivalent of 0.5% w/v of cefoxitin.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution B.

(3) Add 7 mL of *water* and 2 mL of *methanol* to 1 mL of a 0.5% w/v solution of *cefoxitin sodium BPCRS* in solution B. Add 25 mg of *sodium carbonate*, stir for 10 minutes at room temperature, heat in a water-bath at 70° for 30 minutes and allow to cool. Add 3 drops of *glacial acetic acid* and 0.4 mL of a 0.5% w/v solution of *cefoxitin sodium BPCRS* in solution B and mix (generation of cefoxitin lactone).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax SB Phenyl is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A *water*, which has been adjusted to pH 2.7 with *anhydrous formic acid*.

Mobile phase B *acetonitrile*.

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 12	90	10
12 - 37	90 → 80	10 → 20
37 - 50	80 → 60	20 → 40
50 - 55	60 → 20	40 → 80
55 - 60	20	80
60 - 62	20 → 90	80 → 10
62 - 70	90	10

When the chromatograms are recorded under the prescribed conditions the retention time of cefoxitin is about 34 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peak due to cefoxitin and the peak with a retention time relative to cefoxitin of about 1.31 (cefoxitin lactone) is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of not more than three such peaks is greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Water

Not more than 1.0% w/w, Appendix IX C, Method I. Use 0.5 g.

Bacterial endotoxins

www.webofpharma.com

https://thuocngocanh.com/

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of cefoxitin per mL (solution A). The endotoxin limit concentration of solution A is 1.3 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dissolve a quantity of the mixed contents of the 10 containers to produce a solution containing the equivalent of 0.1% w/v of cefoxitin.

(2) 0.1% w/v of *cefoxitin sodium BPCRS*.

(3) 0.08% w/v of *2-(2-thienyl)acetic acid*.

(4) Mix 1 volume of solution (2) and 5 volumes of solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm to 10 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of 5M *acetic acid*, 19 volumes of *acetonitrile* and 81 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the two principal peaks is at least 3.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{17}N_3O_7S_2$ in a container of average content weight from the declared content of $C_{16}H_{16}N_3NaO_7S_2$ in *cefoxitin sodium BPCRS*. Each mg of $C_{16}H_{16}N_3NaO_7S_2$ is equivalent to 0.9510 mg of $C_{16}H_{17}N_3O_7S_2$.

STORAGE

The sealed container should be protected from light and stored at a temperature not exceeding 30°.

LABELLING

The label of the sealed container states the quantity of Cefoxitin Sodium contained in it in terms of the equivalent amount of cefoxitin.

www.webofpharma.com

https://thuathuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuvienthuocngocanh.com/

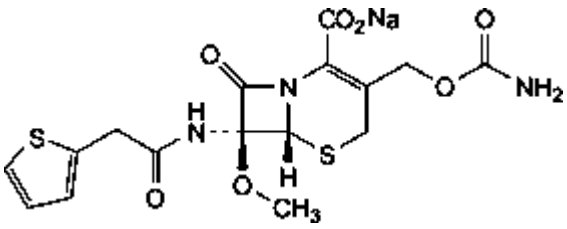
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Cefoxitin Sodium

General Notices

(Ph. Eur. monograph 0990)



$C_{16}H_{16}N_3NaO_7S_2$ 449.4 *33564-30-6*

Action and use

Cephalosporin antibacterial.

Preparation

Cefoxitin Injection

Ph Eur

DEFINITION

Sodium (6*R*,7*S*)-3-[(carbamoyloxy)methyl]-7-methoxy-8-oxo-7-[2-(thiophen-2-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Very soluble in water, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefoxitin sodium CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

pH (*2.2.3*)

4.2 to 7.0.

Dilute 2 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

+ 206 to + 214 (anhydrous substance).

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solution A Dissolve 1.0 g of *potassium dihydrogen phosphate R* and 1.8 g of *anhydrous disodium hydrogen phosphate R* in 1000 mL of *water R*. To 100 mL of the solution add 800 mL of *water R*, adjust to pH 7.0 with *phosphoric acid R* or a 40 g/L solution of *sodium hydroxide R* and dilute to 1000 mL with *water R*.

Test solution Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 20.0 mL with solution A.

Reference solution (c) Dissolve 5 mg of *cefoxitin for peak identification A CRS* (containing impurities A, B, E, F, H, I, J and K) in solution A and dilute to 5 mL with solution A.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (3.0 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: 1.0 g/L solution of *ammonium formate R* adjusted to pH 2.7 with *formic acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	92	8
5 - 50	92 → 74	8 → 26
50 - 85	74	26

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *cefoxitin for peak identification A CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, E+F+K, H, I and J.

Relative retention With reference to cefoxitin (retention time = about 26 min): impurity A = about 0.83; impurity I = about 0.98; impurity H = about 1.06; impurity E or F = about 1.11; impurities [E or F] and K = about 1.16; impurity B = about 1.18; impurity J = about 1.66.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peak due to impurity H and the 1st of the 2 peaks due to impurities E and F;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to cefoxitin.

Limits:

— *impurity I*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *sum of impurities E, F and K*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *impurity H*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity J*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurities A, B*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.0 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 25.0 mg of *cefoxitin sodium CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dissolve 20.0 mg of *2-(2-thienyl)acetic acid R* in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (c) Mix 1.0 mL of reference solution (a) and 5.0 mL of reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetic acid R*, *acetonitrile R*, *water for chromatography R* (1:19:81 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a) and (c).

Run time 12 min.

System suitability Reference solution (c):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 3.5 between the 2 principal peaks.

Calculate the percentage content of $C_{16}H_{16}N_3NaO_7S_2$ taking into account the assigned content of *cefoxitin sodium CRS*.

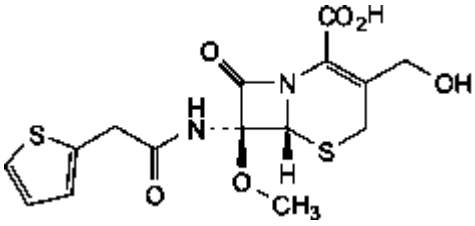
STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

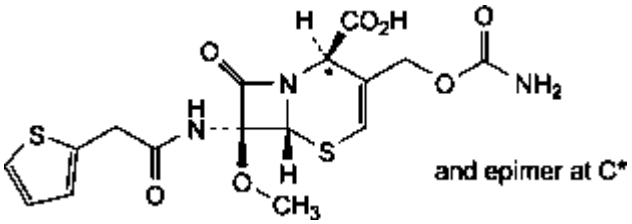
IMPURITIES

Specified impurities *A, B, E, F, H, I, J, K.*

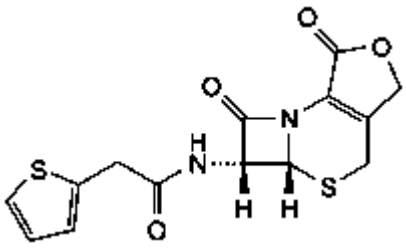
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, G.*



A. (6*R*,7*S*)-3-(hydroxymethyl)-7-methoxy-8-oxo-7-[2-(thiophen-2-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (decarbamoylcefoxitin),



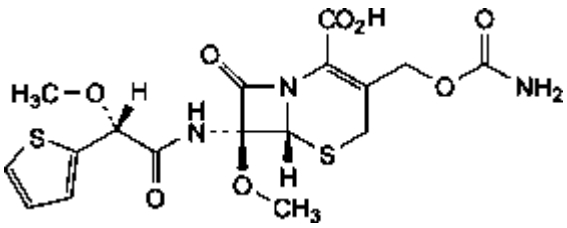
B. (2*RS*,6*R*,7*S*)-3-[(carbamoyloxy)methyl]-7-methoxy-8-oxo-7-[2-(thiophen-2-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid (delta-3-cefoxitin),



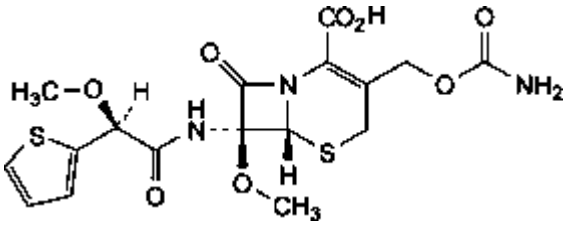
C. *N*-[(5a*R*,6*R*)-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-(thiophen-2-yl)acetamide (cefalotin lactone),

www.webofpharma.com

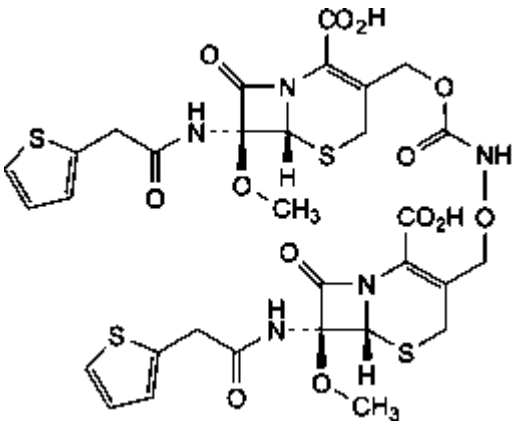
https://thuocngocanh.com/



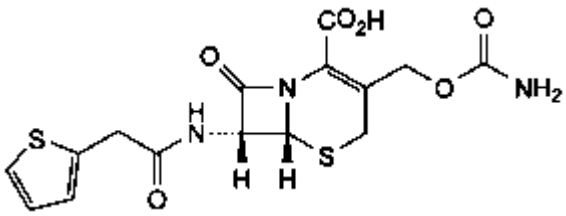
E. (6*R*,7*S*)-3-[(carbamoyloxy)methyl]-7-methoxy-7-[(2*R*)-2-methoxy-2-(thiophen-2-yl)acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid ((*R*)-methoxy cefoxitin),



F. (6*R*,7*S*)-3-[(carbamoyloxy)methyl]-7-methoxy-7-[(2*S*)-2-methoxy-2-(thiophen-2-yl)acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid ((*S*)-methoxy cefoxitin),



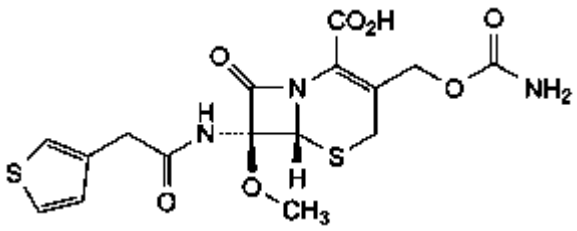
G. (5^6R,5^7S,12^6R,12^7S)-5^7,12^7-dimethoxy-3,5^8,9,12^8,14-pentaoxo-5^5,12^5-dithia-7,10-dioxa-4,5^1,8,12^1,13-pentaaza-1,16(2)-bis(thiophena)-5(7,3),12(3,7)-bis(bicyclo[4.2.0]octana)hexadecaphane-5^2,12^2-diene-5^2,12^2-dicarboxylic acid (cefoxitin dimer),



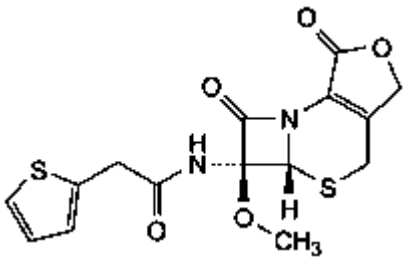
H. (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-8-oxo-7-[2-(thiophen-2-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

www.webofpharma.com

https://thuocngocanh.com/



I. (6*R*,7*S*)-3-[(carbamoyloxy)methyl]-7-methoxy-8-oxo-7-[2-(thiophen-3-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



J. *N*-[(5a*R*,6*S*)-6-methoxy-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-(thiophen-2-yl)acetamide (cefoxitin lactone),

K. unknown structure.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

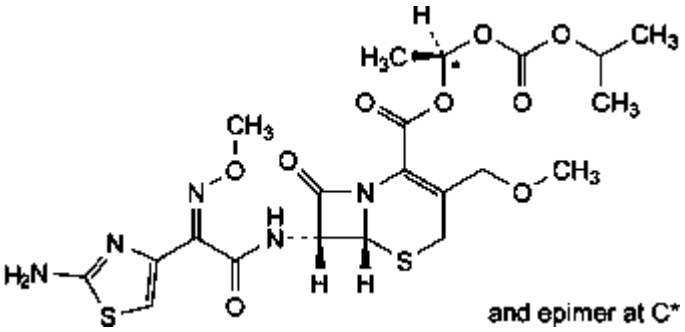
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefpodoxime Proxetil

General Notices

(Ph. Eur. monograph 2341)



$C_{21}H_{27}N_5O_9S_2$ 557.6 *87239-81-4*

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

(1*RS*)-1-[[(1-Methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

94.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow or light brown, amorphous powder.

Solubility

Very slightly soluble or practically insoluble in water, very soluble in acetonitrile and in methanol, freely soluble in anhydrous ethanol.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *cefpodoxime proxetil CRS*.

TESTS

Diastereoisomer ratio

Liquid chromatography (2.2.29) as described under Assay. Use the normalisation procedure.

Limit Test solution:

— the ratio of the area of the peak due to cefpodoxime proxetil diastereoisomer II to the sum of the areas of the peaks due to cefpodoxime proxetil diastereoisomers I and II is between 0.5 and 0.6.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 2-8 °C.*

Solvent mixture *glacial acetic acid R*, *acetonitrile R*, *water R* (2:99:99 *V/V/V*).

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *cefpodoxime proxetil for peak identification CRS* (containing impurities B, C and D) in 5.0 mL of the solvent mixture.

Reference solution (c) Dissolve 5 mg of *cefpodoxime proxetil for impurity H identification CRS* in 5.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: maintain at a constant temperature of 20 °C.

Mobile phase:

— *mobile phase A*: *anhydrous formic acid R*, *methanol R*, *water R* (1:400:600 *V/V/V*);

— *mobile phase B*: *anhydrous formic acid R*, *water R*, *methanol R* (1:50:950 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 65	95	5
65 - 145	95 → 15	5 → 85

www.webofpharma.com

https://thuvienthuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
145 - 155	15	85

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *cefpodoxime proxetil for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C and D; use the chromatogram supplied with *cefpodoxime proxetil for impurity H identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurity H.

Relative retention With reference to cefpodoxime proxetil diastereoisomer II (retention time = about 58 min): diastereoisomer I of impurity B = about 0.68; diastereoisomer I of cefpodoxime proxetil = about 0.74; impurity C = about 0.82; diastereoisomer II of impurity B = about 0.85; impurity D (2 peaks) = about 0.88 and 1.13; peaks due to diastereoisomers of impurity H: between about 1.9 and 2.3.

System suitability:

— the chromatogram obtained with reference solution (b) is similar to the chromatogram supplied with *cefpodoxime proxetil for peak identification CRS*;

— *resolution*: minimum 6.0 between the peaks due to cefpodoxime proxetil diastereoisomers I and II in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.1, where H_p = height above the baseline of the peak due to diastereoisomer II of impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C in the chromatogram obtained with reference solution (b).

Limits:

— *impurity C*: not more than twice the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *impurity D (sum of the 2 diastereoisomers)*: not more than the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *impurity H (sum of the diastereoisomers)*: not more than the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *impurity B (sum of the 2 diastereoisomers)*: not more than 0.5 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *any other impurity*: for each impurity, not more than 0.2 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *total*: not more than 4 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (4.0 per cent);

— *disregard limit*: 0.05 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (*2.2.29*).

Solution A 20 mg/L solution of *anhydrous citric acid R* in *acetonitrile R*.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution Dissolve 30.0 mg of *cefpodoxime proxetil CRS* in solution A and dilute to 50.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *methanol R*, *water R* (9:11 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time 1.2 times the retention time of cefpodoxime proxetil diastereoisomer II.

Retention time Cefpodoxime proxetil diastereoisomer II = about 30 min.

System suitability Reference solution:

— *resolution*: minimum 4.0 between the peaks due to cefpodoxime proxetil diastereoisomers I and II.

Calculate the percentage content of $C_{21}H_{27}N_5O_9S_2$ from the sum of the areas of the 2 peaks due to the diastereoisomers and using the declared content of *cefpodoxime proxetil CRS*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

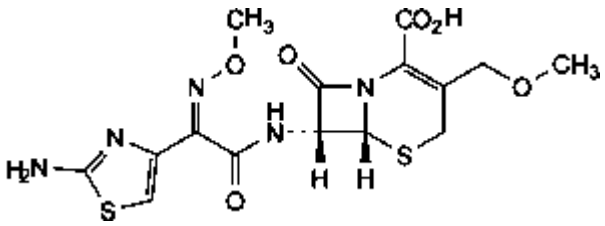
STORAGE

Protected from light.

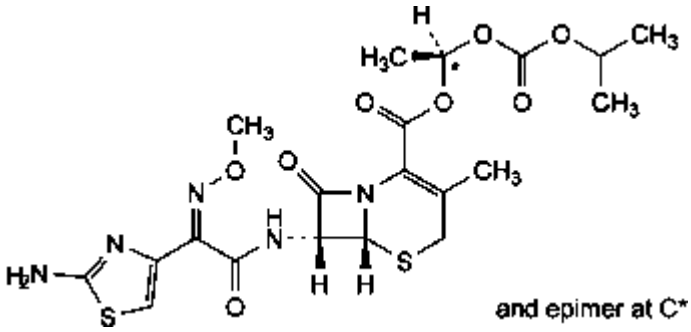
IMPURITIES

Specified impurities *B, C, D, H.*

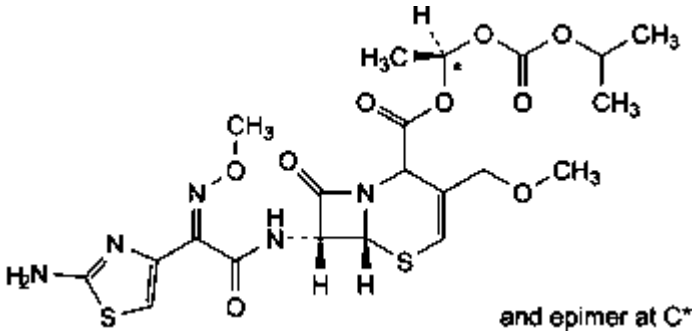
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, E, F, G.*



A. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefpodoxime),



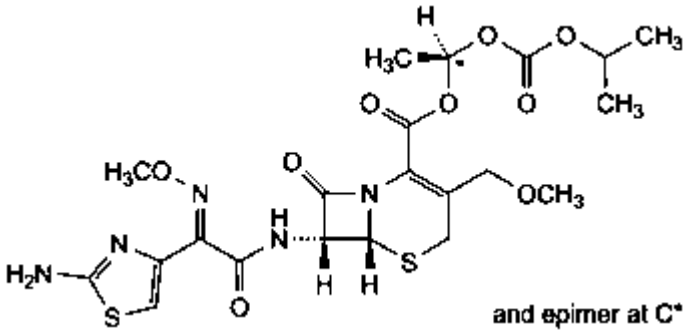
B. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (ADCA-analogue of cefpodoxime proxetil),



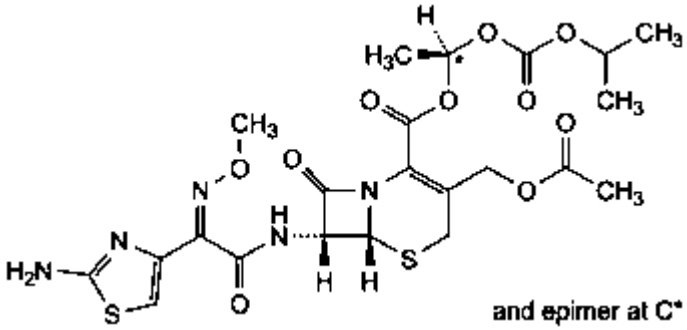
C. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (delta-2-cefpodoxime proxetil),

www.webofpharma.com

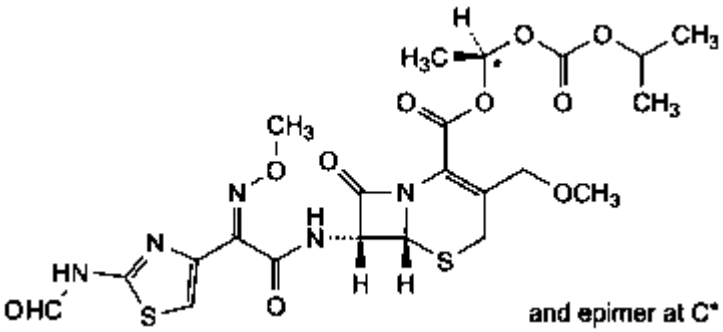
https://thuocngocanh.com/



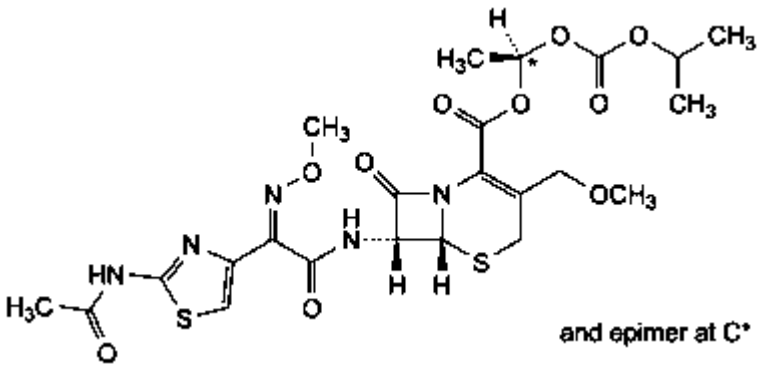
D. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*E*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (anti-cefpodoxime proxetil),



E. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-3-(acetoxymethyl)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (ACA-analogue of cefpodoxime proxetil),



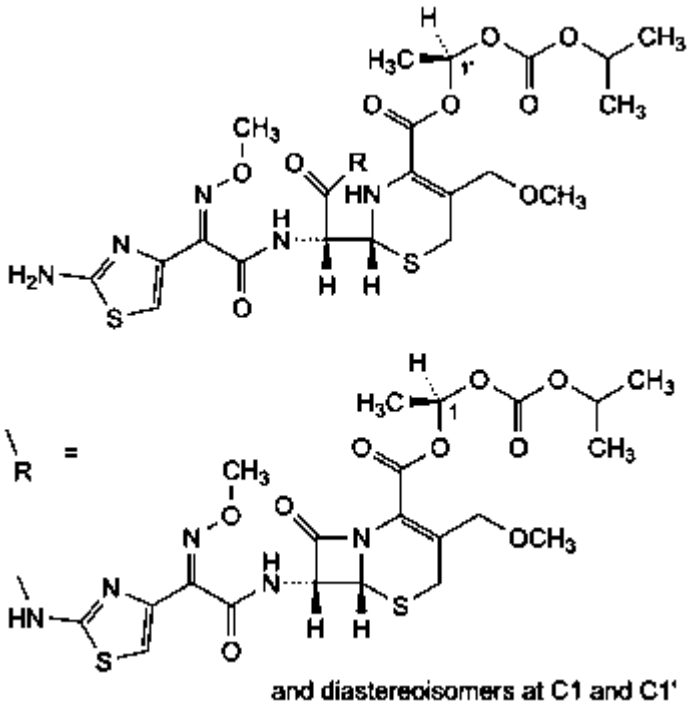
F. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-[(2-formylamino)thiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (*N*-formyl cefpodoxime proxetil),



www.webofpharma.com

https://thuocngocanh.com/

G. (1*RS*)-1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-[2-(2-acetylamino)thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (*N*-acetyl-cefpodoxime proxetil),



H. mixture of the diastereoisomers of 1-[[(1-methylethoxy)carbonyl]oxy]ethyl (6*R*,7*R*)-7-[[(2*Z*)-2-[2-[[(2*R*)-2-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-2-[(2*R*)-5-(methoxymethyl)-4-[[1-[[(1-methylethoxy)carbonyl]oxy]ethoxy]carbonyl]-3,6-dihydro-2*H*-1,3-thiazin-2-yl]acetyl]amino]thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (cefpodoxime proxetil dimer).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

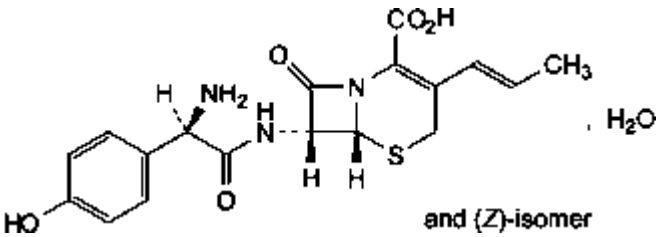
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefprozil Monohydrate

General Notices

(Ph. Eur. monograph 2342)



$C_{18}H_{19}N_3O_5S, H_2O$ 407.4 *121123-17-9*

Action and use

Cephalosporin antibacterial.

Ph Eur

DEFINITION

Mixture of the 2 diastereoisomers of (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-[(1*EZ*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellow, crystalline powder, slightly hygroscopic.

Solubility

Slightly soluble in water and in methanol, practically insoluble in acetone.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *cefprozil CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 0.125 g of the substance to be examined in 1 mL of a 103 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with mobile phase A.

Test solution (b) Dissolve 30.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of *cefprozil for peak identification CRS* (containing impurities B, H and M) in 0.05 mL of a 103 g/L solution of *hydrochloric acid R* and add 1 mL of mobile phase A.

Reference solution (c) Dissolve 3 mg of *cefprozil CRS* and 6 mg of *cefprozil impurity mixture CRS* (containing impurities D and F) in 2 mL of a 103 g/L solution of *hydrochloric acid R* and dilute to 50 mL with mobile phase A.

Reference solution (d) Dissolve 30.0 mg of *cefprozil CRS* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (e) Dissolve 10.0 mg of *cefadroxil CRS* (impurity B) in *water R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 20.0 mL with *water R*.

Reference solution (f) Dissolve 10.0 mg of *cefprozil impurity A CRS* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 11.5 g of *ammonium dihydrogen phosphate R* in *water for chromatography R*, adjust to pH 4.4 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*, mobile phase A (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	81	19

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	36	64
20 - 25	36	64

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b), (c), (e) and (f).

Identification of impurities Use the chromatogram supplied with *cefprozil for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, H and M; use the chromatogram supplied with *cefprozil impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and F; impurities G and I are identified by their relative retention.

Relative retention With reference to cefprozil (*Z*)-isomer (retention time = about 7 min): impurity A = about 0.4; impurity B = about 0.5; impurity D = about 0.7; impurity F = about 0.9; cefprozil (*E*)-isomer = about 1.4; impurity G = about 1.7; impurity H = about 2.0; impurity I = about 2.1; impurity M = about 2.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.4 between the peaks due to impurity F and cefprozil (*Z*)-isomer.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity D by 2.3;

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.5 per cent);

— *impurities D, G, H, I, M*: for each impurity, not more than 0.3 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (f) (0.2 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *total*: maximum 2.0 per cent;

— *disregard limit*: 0.05 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.05 per cent).

(*E*)-isomer ratio

Liquid chromatography (*2.2.29*) as described under Assay.

Determine the area of the peak due to the (*E*)-isomer in the chromatogram obtained with test solution (b) and reference solution (d). Calculate the ratio of the (*E*)-isomer to the sum of both cefprozil isomers, as determined under Assay.

www.webofpharma.com

https://thuocngocanh.com/

Limit:

— *(E)-isomer ratio*: 0.06 to 0.11.

Water (2.5.12)

3.5 per cent to 6.5 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (18:82 *V/V*).

Detection Spectrophotometer at 280 nm.

Injection 10 µL of test solution (b) and reference solution (d).

Run time Twice the retention time of cefprozil (*Z*)-isomer.

Elution order (*Z*)-isomer, (*E*)-isomer.

Retention time Cefprozil (*Z*)-isomer = about 8 min.

System suitability Reference solution (d):

— *resolution*: minimum 2.5 between the peaks due to cefprozil (*Z*)-isomer and the (*E*)-isomer.

Calculate the percentage content of the sum of both isomers of cefprozil ($C_{18}H_{19}N_3O_5S$) taking into account the assigned contents of both (*E*)-isomer and (*Z*)-isomer of *cefprozil CRS*.

STORAGE

In an airtight container.

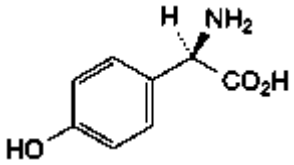
IMPURITIES

Specified impurities *A, B, D, G, H, I, M.*

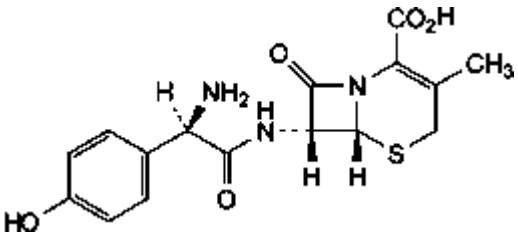
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, F, J, K, L, N.*

www.webofpharma.com

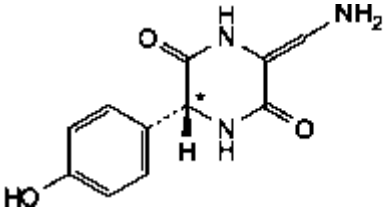
https://thuocngocanh.com/



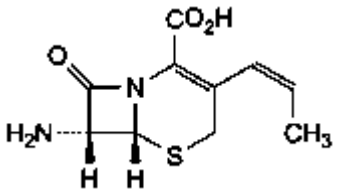
A. (2*R*)-2-amino-2-(4-hydroxyphenyl)acetic acid (*p*-hydroxyphenylglycine),



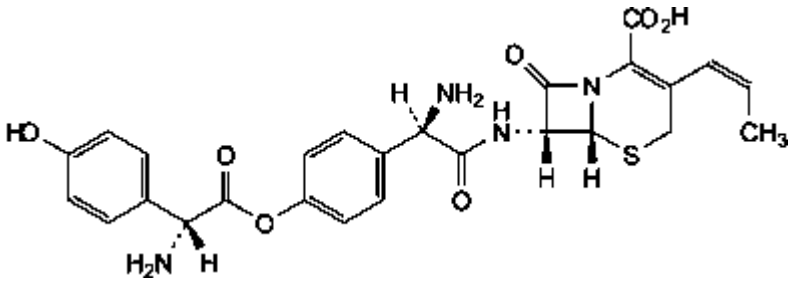
B. (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefadroxil),



C. (6*RS*)-3-(aminomethylene)-6-(4-hydroxyphenyl)piperazine-2,5-dione,



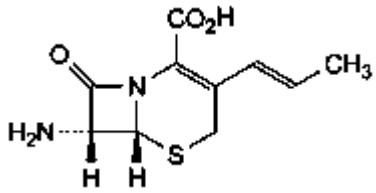
D. (6*R*,7*R*)-7-amino-8-oxo-3-[(1*Z*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



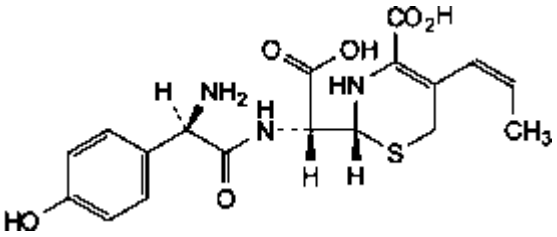
E. (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-[4-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]oxy]phenyl]acetyl]amino]-8-oxo-3-[(1*Z*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

www.webofpharma.com

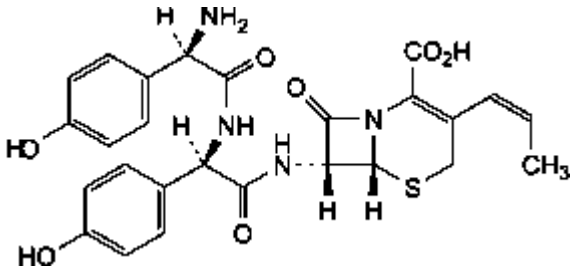
https://thuocngocanh.com/



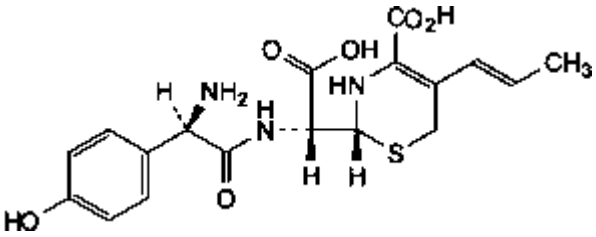
F. (6*R*,7*R*)-7-amino-8-oxo-3-[(1*E*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



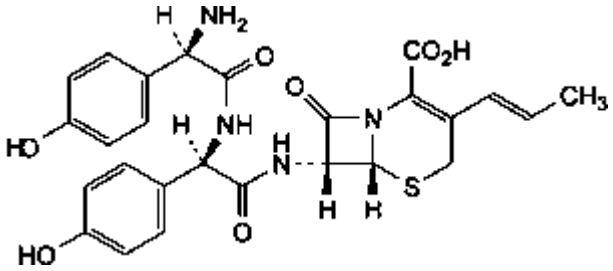
G. (2*R*)-2-[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino-2-[(2*R*)-4-carboxy-5-[(1*Z*)-prop-1-enyl]-3,6-dihydro-2*H*-1,3-thiazin-2-yl]-acetic acid,



H. (6*R*,7*R*)-7-[[(2*R*)-2-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-[(1*Z*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



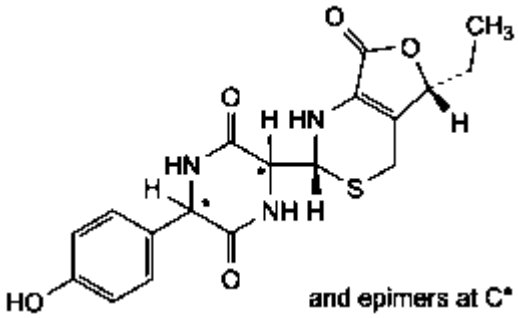
I. (2*R*)-2-[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino-2-[(2*R*)-4-carboxy-5-[(1*E*)-prop-1-enyl]-3,6-dihydro-2*H*-1,3-thiazin-2-yl]-acetic acid,



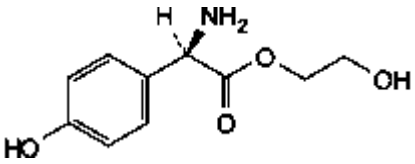
J. (6*R*,7*R*)-7-[[(2*R*)-2-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-[(1*E*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

www.webofpharma.com

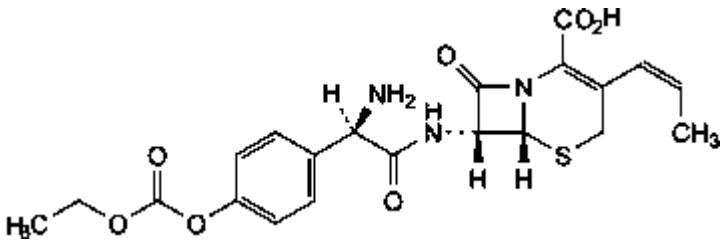
https://thuocngocanh.com/



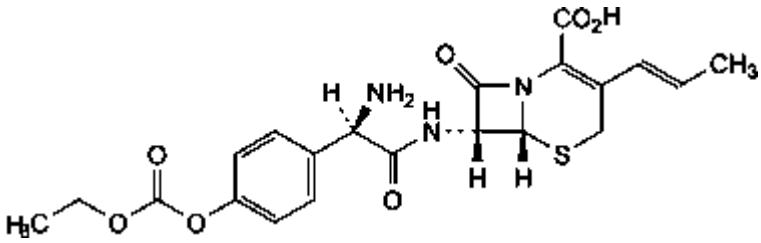
K. mixture of 4 diastereoisomers of (3*RS*,6*RS*)-3-[(2*R*,5*R*)-5-ethyl-7-oxo-1,2,5,7-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-yl]-6-(4-hydroxyphenyl)piperazine-2,5-dione,



L. 2-hydroxyethyl (2*R*)-2-amino-2-(4-hydroxyphenyl)acetate,



M. (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-[4-[(ethoxycarbonyl)oxy]phenyl]acetyl]amino]-8-oxo-3-[(1*Z*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



N. (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-[4-(ethoxycarbonyl)oxy]phenyl]acetyl]amino]-8-oxo-3-[(1*E*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

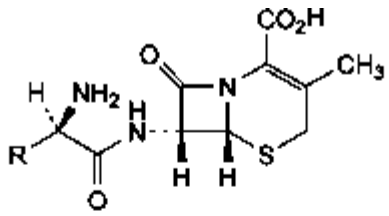
https://thuocngocanh.com/

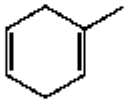
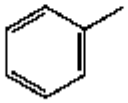
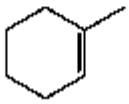
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefradine

General Notices

(Ph. Eur. monograph 0814)



Compound	R	Mol. Formula	M_r
cefradine		$C_{16}H_{19}N_3O_4S$	349.4
cefalexin		$C_{16}H_{17}N_3O_4S$	347.4
4',5'-dihydrocefradine		$C_{16}H_{21}N_3O_4S$	351.4

Cefradine *38821-53-3*

Action and use

Cephalosporin antibacterial.

Preparations

Cefradine Capsules

Cefradine Injection

Cefradine Oral Suspension

Ph Eur

DEFINITION

Main component (6*R*,7*R*)-7-[[(2*R*)-amino(cyclohexa-1,4-dienyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefradine).

Semi-synthetic product derived from a fermentation product.

www.webofpharma.com

https://thuocngocanh.com/

Content

— *cefradine*: minimum 90.0 per cent (anhydrous substance);

— *cefalexin*: maximum 5.0 per cent (anhydrous substance);

— *4',5'-dihydrocefradine*: maximum 2.0 per cent (anhydrous substance);

— *sum of the percentage contents of cefradine, cefalexin and 4',5'-dihydrocefradine*: 96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow, hygroscopic powder.

Solubility

Sparingly soluble in water, practically insoluble in ethanol (96 per cent) and in hexane.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cefradine CRS*.

If the spectra obtained in the solid state show differences, dissolve 30 mg of the substance to be examined and 30 mg of the reference substance separately in 10 mL of *methanol R*, evaporate to dryness at 40 °C at a pressure less than 2 kPa and record new spectra using the residues.

TESTS

Solution S

Dissolve 2.50 g in *sodium carbonate solution R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*). Allow solution S to stand for 5 min. The absorbance (*2.2.25*) of solution S measured at 450 nm is not greater than 0.60.

pH (*2.2.3*)

3.5 to 6.0.

Dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

www.webofpharma.com

https://thuocngocanh.com/

+ 80.0 to + 90.0 (anhydrous substance).

Dissolve 0.250 g in *acetate buffer solution pH 4.6 R* and dilute to 25.0 mL with the same solution.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.300 g of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 3.0 mg of *cyclohexa-1,4-dienylglycine CRS* (impurity B) in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (b) Dissolve 3 mg of the substance to be examined and 3 mg of *cefalexin monohydrate CRS* in mobile phase A and dilute to 25 mL with mobile phase A.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (d) Dissolve 6 mg of *cefradine for peak identification CRS* (containing impurities C, D and E) in 1.0 mL of mobile phase A.

Reference solution (e) Dissolve the contents of a vial of *cefradine impurity mixture CRS* (impurities A and G) in 1.0 mL of mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 2.72 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *dilute phosphoric acid R*;

— *mobile phase B*: *methanol R2*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.5	99.5 → 97	0.5 → 3
2.5 - 11	97 → 75	3 → 25
11 - 13	75 → 60	25 → 40
13 - 16	60	40
16 - 19	60 → 20	40 → 80

www.webofpharma.com

https://thuvienthuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
19 - 19.1	20 → 99.5	80 → 0.5
19.1 - 25	99.5	0.5

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 25 µL.

Identification of impurities Use the chromatogram supplied with *cefradine for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities C, D and E; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B; use the chromatogram supplied with *cefradine impurity mixture CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A and G.

Relative retention With reference to cefradine (retention time = about 15 min): impurity A = about 0.27; impurity B = about 0.32; impurity C = about 0.53; impurity D = about 0.63; impurity E = about 0.80; impurity F = about 0.92; cefalexin = about 0.95; 4′,5′-dihydrocefradine = about 1.06; impurity G = about 1.32.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to cefalexin and cefradine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 3.4;

— *impurities A, B, C, D, E, F, G*: for each impurity, not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.25 per cent);

— *any other impurity*: for each impurity, not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.25 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard the peaks due to cefalexin and 4′,5′-dihydrocefradine.

N,*N*-Dimethylaniline (*2.4.26, Method B*)

Maximum 20 ppm.

Water (*2.5.12*)

Maximum 6.0 per cent, determined on 0.300 g.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in *phosphate buffer solution pH 5.0 R* and dilute to 100.0 mL with the same solution.

Reference solution (a) Dissolve 50.0 mg of *cefradine CRS* (containing 4′,5′-dihydrocefradine) in *phosphate buffer solution pH 5.0 R* and dilute to 100.0 mL with the same solution.

Reference solution (b) Dissolve 5.0 mg of *cefalexin monohydrate CRS* in *phosphate buffer solution pH 5.0 R* and dilute to 100.0 mL with the same solution.

Reference solution (c) Dilute 1 mL of reference solution (a) to 10 mL with *phosphate buffer solution pH 5.0 R*. Mix 5 mL of this solution and 5 mL of reference solution (b).

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, *phosphate buffer solution pH 5.0 R* (25:75 *V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 5 µL.

Run time Twice the retention time of cefradine.

Relative retention With reference to cefradine (retention time = about 3 min): cefalexin = about 0.7; 4′,5′-dihydrocefradine = about 1.5.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to cefalexin and cefradine.

Calculate the percentage content of cefradine using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *cefradine CRS*. Calculate the percentage content of cefalexin using the chromatogram obtained with reference solution (b) and taking into account the assigned content of *cefalexin monohydrate CRS*. Calculate the percentage content of 4′,5′-dihydrocefradine using the chromatogram obtained with reference solution (b), taking into account the assigned content of *cefalexin monohydrate CRS* and multiplying the area of the peak due to 4′,5′-dihydrocefradine by a correction factor of 1.6.

www.webofpharma.com

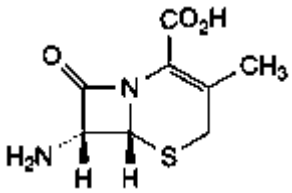
https://thuvienthuocngocanh.com/

STORAGE

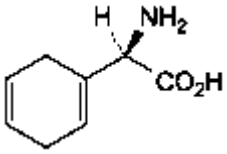
In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

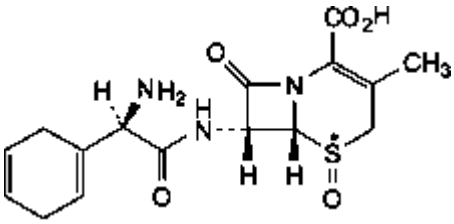
Specified impurities *A, B, C, D, E, F, G.*



A. (6*R*,7*R*)-7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-aminodeacetoxycephalosporanic acid, 7-ADCA),

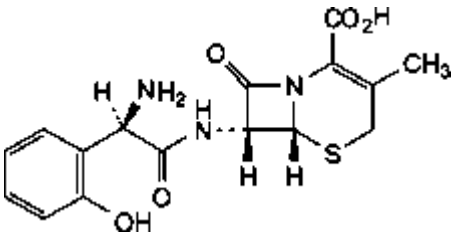


B. (2*R*)-amino(cyclohexa-1,4-dienyl)acetic acid (D-dihydrophenylglycine, cyclohexa-1,4-dienylglycine),



C. (6*R*,7*R*)-7-[[(2*R*)-amino(cyclohexa-1,4-dienyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 5-oxide (isomer 1),

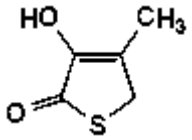
D. (6*R*,7*R*)-7-[[(2*R*)-amino(cyclohexa-1,4-dienyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 5-oxide (isomer 2),



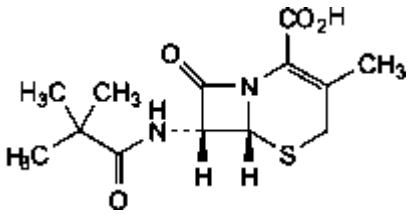
E. (6*R*,7*R*)-7-[[(2*R*)-amino(2-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

www.webofpharma.com

https://thuocngocanh.com/



F. 3-hydroxy-4-methylthiophen-2(5*H*)-one,



G. (6*R*,7*R*)-7-[(2,2-dimethylpropanoyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ADCA pivalamide).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefradine Capsules

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefradine Capsules contain Cefradine.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of cephalosporins, calculated as the sum of cefradine ($C_{16}H_{19}N_3O_4S$), cefalexin ($C_{16}H_{17}N_3O_4S$) and 4′,5′-dihydrocefradine ($C_{16}H_{21}N_3O_4S$)

90.0 to 105.0% of the stated amount of Cefradine.

IDENTIFICATION

A. The *infrared absorption spectrum* of the contents of the capsules, Appendix II A, is concordant with the *reference spectrum* of cefradine *(RS 050)*. If the spectra are not concordant, dissolve a quantity of the capsule contents containing 30 mg of Cefradine in 10 mL of *methanol*, evaporate to dryness at 40° at a pressure of 2 kPa and prepare a new spectrum.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 0.1 g of Cefradine with 25 mL of 0.01M *ammonia* for 45 minutes and dilute 1 mL of the resulting solution to 10 mL with 0.01M *ammonia*.

(2) 0.040% w/v of *cefradine BPCRS* in 0.01M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Analtech plates are suitable). Impregnate the plate by placing it in a tank containing a shallow layer of a 5% v/v solution of n-*tetradecane* in n-*hexane*, allowing the impregnating solvent to ascend to the top, removing the plate from the tank and allowing the solvent to evaporate; use with the flow of the mobile phase in the same direction that the impregnation was carried out.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, heat at 90° for 2 to 3 minutes and spray the hot plate with a 0.1% w/v solution of *ninhydrin* in the mobile phase. Heat at 90° for 15 minutes in a circulating air oven with the plates parallel to the airflow, cool for 15 minutes protected from light and examine in daylight.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

3 volume of *acetone*, 80 volumes of 0.2M *anhydrous disodium hydrogen orthophosphate* and 120 volumes of 0.1M *citric acid*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.12M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium, filter and dilute the filtered solution, if necessary, with sufficient 0.12M *hydrochloric acid* to produce a solution expected to contain about 0.0025% w/v of Cefradine. Measure the *absorbance* of the filtered sample at the maximum at 255 nm, Appendix II B, using 0.12M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a 0.0025% w/v solution of *cefradine BPCRS* in 0.12M *hydrochloric acid* using 0.12M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of cephalosporins, as the sum of the contents of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$ in the medium from the *absorbance* obtained and using the declared content of total cephalosporins in *cefradine BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 0.3 g of Cefradine in mobile phase A, add sufficient mobile phase A to produce 50 mL and filter through a 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) 0.012% w/v of each of *cefradine BPCRS* and *cefalexin BPCRS* in mobile phase A.

(4) 0.003% w/v of *cyclohexa-1,4-dienylglycine EPCRS* (impurity B) in mobile phase A.

(5) Dissolve 6 mg of *cefradine for peak identification EPCRS* (containing impurities C, D and E) in 1 mL of mobile phase A.

(6) Dissolve the contents of a vial of *cefradine impurity mixture EPCRS* (containing impurities A and G) in 1 mL of mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Varian Chrompack Inertsil ODS-3 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 0.272% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 with *dilute orthophosphoric acid*.

Mobile phase B *methanol R2*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	99.5→97	0.5→3	linear gradient
2.5-11	97→75	3→25	linear gradient
11-13	75→60	25→40	linear gradient
13-16	60	40	isocratic
16-19	60→20	40→80	linear gradient
19-19.1	20→99.5	80→0.5	linear gradient
19.1-25	99.5	0.5	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to Cefradine (retention time = about 15 minutes) are: impurity A = about 0.27; impurity B = about 0.32; impurity C = about 0.53; impurity D = about 0.63; impurity E = about 0.80; impurity F = about 0.92; cefalexin = about 0.95; 4′,5′-dihydrocefradine = about 1.06; impurity G = about 1.32.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefalexin and cefradine is at least 4.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) due to impurities C, D and E using the chromatogram obtained with solution (5) and the chromatogram supplied with *cefradine for peak identification EPCRS*. Identify any peaks in the chromatogram obtained with solution (1) due to impurities A and G using the chromatogram obtained with solution (6) and the chromatogram supplied with *cefradine impurity mixture EPCRS*. Identify any peak in the chromatogram obtained with solution (1) due to impurity B using the chromatogram obtained with solution (4). Multiply the area of any peak corresponding to impurity B by the following correction factor: 3.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A, B, D, F or G is not greater than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.25% for each);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity C is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard the peaks due to cefalexin, and 4′,5′-dihydrocefradine and any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Cefalexin

Not more than 10.0%, calculated as the percentage of $C_{16}H_{17}N_3O_4S$ in the sum of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$ determined in the Assay.

4′,5′-Dihydrocefradine

Not more than 2.0%, calculated as the percentage of $C_{16}H_{21}N_3O_4S$ in the sum of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$ determined in the Assay.

Loss on drying

The contents of the capsules, when dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, lose not more than 7.0% of their weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 3 volumes of 0.7M *glacial acetic acid*, 15 volumes of 0.5M *sodium acetate*, 200 volumes of *methanol* and 782 volumes of *water* (solution A).

(1) Dissolve a quantity of the powdered mixed contents of 20 capsules to produce a solution containing 0.05% w/v of Cefradine.
(2) 0.05% w/v of *cefradine BPCRS*.
(3) 0.005% w/v of *cefalexin BPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes with solution A. Mix equal volumes of this solution and solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.

www.webofpharma.com

https://thuathuocngocanh.com/

(e) Use a detection wavelength of 254 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

25 volumes of *methanol* and 75 volumes of *phosphate buffer solution pH 5.0*.

When the chromatograms are recorded under the prescribed conditions, the retention time of the peak due to 4',5'-dihydrocefradine relative to that of cefradine is about 1.6.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to cefradine and cefalexin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of cephalosporins in the capsules by determining the sum of the contents of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$. Calculate the content of $C_{16}H_{19}N_3O_4S$ (cefradine) using the declared content of $C_{16}H_{19}N_3O_4S$ in *cefradine BPCRS*. Calculate the content of $C_{16}H_{17}N_3O_4S$ (cefalexin) using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS*. Calculate the content of $C_{16}H_{21}N_3O_4S$ (4′,5′-dihydrocefradine) using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS* and multiplying the area of the peak due to 4′,5′-dihydrocefradine by a correction factor of 1.6.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Cefradine.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefradine Injection

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefradine Injection is a sterile solution of Cefradine in Water for Injections. It is prepared by dissolving Cefradine for Injection in the requisite amount of Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Cefradine Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

CEFRADINE FOR INJECTION

DEFINITION

Cefradine for Injection is a sterile material consisting of Cefradine with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of cephalosporins, calculated as the sum of cefradine ($C_{16}H_{19}N_3O_4S$), cefalexin ($C_{16}H_{17}N_3O_4S$) and 4′,5′-dihydrocefradine ($C_{16}H_{21}N_3O_4S$)

95.0 to 110.0% of the stated amount of Cefradine.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of a sealed container in sufficient *water* to produce a solution containing 0.3% w/v of Cefradine.

(2) 0.3% w/v of *cefradine BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Analtech plates are suitable). Impregnate the plate by placing it in a tank containing a shallow layer of a 5% v/v solution of n-*tetradecane* in n-*hexane*, allowing the impregnating solvent to ascend to the top, removing the plate from the tank and

www.webofpharma.com

https://thuocngocanh.com/

allowing the solvent to evaporate; use with the flow of the mobile phase in the same direction that the impregnation was carried out.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry at 105° and examine in daylight.

MOBILE PHASE

3 volumes of a 6.7% w/v solution of *ninhydrin* in *acetone*, 80 volumes of 0.1M *anhydrous disodium hydrogen orthophosphate* and 120 volumes of 0.1M *citric acid*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH of a solution containing 1% w/v of Cefradine, 8.0 to 9.6, Appendix V L.

Clarity and colour of solution

A solution containing 13.6% w/v of Cefradine in *water* is *clear*, Appendix IV A. The *absorbance* of the solution at 450 nm is not greater than 0.6, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the contents of a sealed container containing 0.3 g of Cefradine in mobile phase A and add sufficient mobile phase A to produce 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) 0.012% w/v of each of *cefradine BPCRS* and *cefalexin BPCRS* in mobile phase A.

(4) 0.003% w/v of *cyclohexa-1,4-dienylglycine EPCRS* (impurity B) in mobile phase A.

(5) Dissolve 6 mg of *cefradine for peak identification EPCRS* (containing impurities C, D and E) in 1 mL of mobile phase A.

(6) Dissolve the contents of a vial of *cefradine impurity mixture EPCRS* (containing impurities A and G) in 1 mL of mobile phase A.

(7) 0.1% w/v of *arginine* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Varian Chrompack Inertsil ODS-3 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 0.272% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 with *dilute orthophosphoric acid*.

Mobile phase B *methanol R2*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	99.5→97	0.5→3	linear gradient
2.5-11	97→75	3→25	linear gradient
11-13	75→60	25→40	linear gradient
13-16	60	40	isocratic
16-19	60→20	40→80	linear gradient
19-19.1	20→99.5	80→0.5	linear gradient
19.1-25	99.5	0.5	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to Cefradine (retention time = about 15 minutes) are: impurity A = about 0.27; impurity B = about 0.32; impurity C = about 0.53; impurity D = about 0.63; impurity E = about 0.80; impurity F = about 0.92; cefalexin = about 0.95; 4′,5′-dihydrocefradine = about 1.06; impurity G = about 1.32.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefalexin and cefradine is at least 4.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) due to impurities C, D and E using the chromatogram obtained with solution (5) and the chromatogram supplied with *cefradine for peak identification EPCRS*. Identify any peaks in the chromatogram obtained with solution (1) due to impurities A and G using the chromatogram obtained with solution (6) and the chromatogram supplied with *cefradine impurity mixture EPCRS*. Identify any peak in the chromatogram obtained with solution (1) due to impurity B using the chromatogram obtained with solution (4). Multiply the area of any peak corresponding to impurity B by the following correction factor: 3.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A, B, C, D, E, F or G is not greater than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.25% for each);

www.webofpharma.com

https://thuocngocanh.com/

the area of any other *secondary peak* is not greater than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard the peaks due to cefalexin, 4′,5′-dihydrocefradine and any peak corresponding to the principal peak in the chromatogram obtained with solution (7) (arginine) and any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Cefalexin

Not more than 5.0%, calculated as the percentage of $C_{16}H_{17}N_3O_4S$ in the sum of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$ determined in the Assay.

4′,5′-Dihydrocefradine

Not more than 2.0%, calculated as the percentage of $C_{16}H_{21}N_3O_4S$ in the sum of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$ determined in the Assay.

Water

Not more than 5.0% w/w, Appendix IX C. Use 0.4 g.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parental Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 3 volumes of 0.7M *glacial acetic acid*, 15 volumes of 0.5M *sodium acetate*, 200 volumes of *methanol* and 782 volumes of *water* (solution A).

(1) Dissolve a quantity of the mixed contents of the 10 containers in sufficient of solution A to produce a solution containing 0.05% w/v of Cefradine.
(2) 0.05% w/v of *cefradine BPCRS*.
(3) 0.005% w/v of *cefalexin BPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes with solution A. Mix equal volumes of this solution and solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 5 µL of each solution.

MOBILE PHASE

25 volumes of *methanol* and 75 volumes of *phosphate buffer solution pH 5.0*.

When the chromatograms are recorded under the prescribed conditions, the retention time of the peak due to 4',5'-dihydrocefradine relative to that of cefradine is about 1.6.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to cefradine and cefalexin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of cephalosporins in a container of average content weight by determining the sum of the contents of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$. Calculate the content of $C_{16}H_{19}N_3O_4S$ (cefradine) using the declared content of $C_{16}H_{19}N_3O_4S$ in *cefradine BPCRS*. Calculate the content of $C_{16}H_{17}N_3O_4S$ (cefalexin) using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS*. Calculate the content of $C_{16}H_{21}N_3O_4S$ (4′,5′-dihydrocefradine) using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS* and multiplying the area of the peak due to 4′,5′-dihydrocefradine by a correction factor of 1.6.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Cefradine.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefradine Oral Suspension

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefradine Oral Suspension is a suspension of Cefradine in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of Water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for the Preparation of Oral Liquids stated under Oral Liquids.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of cephalosporins, calculated as the sum of cefradine ($C_{16}H_{19}N_3O_4S$), cefalexin ($C_{16}H_{17}N_3O_4S$) and 4′,5′-dihydrocefradine ($C_{16}H_{21}N_3O_4S$)

When freshly constituted, not more than 110.0% of the stated amount of Cefradine. When stored at the temperature and for the period stated on the label during which the Oral Suspension may be expected to be satisfactory for use, not less than 90.0% of the stated amount of Cefradine.

IDENTIFICATION

A. Shake a quantity of the oral suspension containing 25 mg of Cefradine with 100 mL of *water*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum at 261 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the oral suspension with sufficient *water* to produce a solution containing 0.3% w/v of Cefradine, filter and use the filtrate.

(2) 0.3% w/v of *cefradine BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Analtech plates are suitable). Impregnate the plate by placing it in a tank containing a shallow layer of a 5% v/v solution of n-*tetradecane* in n-*hexane*, allowing the impregnating solvent to ascend to the top, removing the plate from the tank and allowing the solvent to evaporate; use with the flow of the mobile phase in the same direction that the impregnation was carried out.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate allow it to dry at 105° and examine in daylight.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

3 volumes of a 6.7% w/v solution of *ninhydrin* in *acetone*, 80 volumes of 0.1M *anhydrous disodium hydrogen orthophosphate* and 120 volumes of 0.1M *citric acid*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the oral suspension containing 0.3 g of Cefradine in mobile phase A, add sufficient mobile phase A to produce 50 mL and filter through a 0.45-µm filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.
(3) 0.012% w/v of each of *cefradine BPCRS* and *cefalexin BPCRS* in mobile phase A.
(4) 0.003% w/v of *cyclohexa-1,4-dienylglycine EPCRS* (impurity B) in mobile phase A.
(5) Dissolve 6 mg of *cefradine for peak identification EPCRS* (containing impurities C, D and E) in 1 mL of mobile phase A.
(6) Dissolve the contents of a vial of *cefradine impurity mixture EPCRS* (containing impurities A and G) in 1 mL of mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Varian Chrompack Inertsil ODS-3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 0.272% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 with *dilute orthophosphoric acid*.

Mobile phase B *methanol R2*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2.5	99.5→97	0.5→3	linear gradient
2.5-11	97→75	3→25	linear gradient
11-13	75→60	25→40	linear gradient
13-16	60	40	isocratic
16-19	60→20	40→80	linear gradient
19-19.1	20→99.5	80→0.5	linear gradient
19.1-25	99.5	0.5	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to Cefradine (retention time = about 15 minutes) are: impurity A = about 0.27; impurity B = about 0.32; impurity C = about 0.53; impurity D = about 0.63; impurity E = about 0.80; impurity F = about 0.92; cefalexin = about 0.95; 4′,5′-dihydrocefradine = about 1.06; impurity G = about 1.32.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cefalexin and cefradine is at least 4.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) due to impurities C, D and E using the chromatogram obtained with solution (5) and the chromatogram supplied with *cefradine for peak identification EPCRS*. Identify any peaks in the chromatogram obtained with solution (1) due to impurities A and G using the chromatogram obtained with solution (6) and the chromatogram supplied with *cefradine impurity mixture EPCRS*. Identify any peak in the chromatogram obtained with solution (1) due to impurity B using the chromatogram obtained with solution (4). Multiply the area of any peak corresponding to impurity B by the following correction factor: 3.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A, B, C, D, F or G is not greater than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.25% for each);

the area of any peak corresponding to impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

www.webofpharma.com

https://thuocngocanh.com/

Disregard the peaks due to cefalexin, and 4′,5′-dihydrocefradine and any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Cefalexin

Not more than 10.0%, calculated as the percentage of $C_{16}H_{17}N_3O_4S$ in the sum of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$ determined in the Assay.

4′,5′-Dihydrocefradine

Not more than 2.0%, calculated as the percentage of $C_{16}H_{21}N_3O_4S$ in the sum of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$ determined in the Assay.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 3 volumes of 0.7M *glacial acetic acid*, 15 volumes of 0.5M *sodium acetate*, 200 volumes of *methanol* and 782 volumes of *water* (solution A).

(1) Shake a weighed quantity of the oral suspension with sufficient of the mobile phase to produce a solution containing 0.05% w/v of Cefradine and filter through a 0.5-µm filter, discarding the first few mL of filtrate.
(2) 0.05% w/v of *cefradine BPCRS*.
(3) 0.005% w/v of *cefalexin BPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes with solution A. Mix equal volumes of this solution and solution (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 5 µL of each solution.

MOBILE PHASE

25 volumes of *methanol* and 75 volumes of *phosphate buffer solution pH 5.0*.

When the chromatograms are recorded under the prescribed conditions, the retention time of the peak due to 4',5'-dihydrocefradine relative to that of cefradine is about 1.6.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to cefradine and cefalexin is at least 4.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuathuocngocanh.com/

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of cephalosporins, weight in volume, by determining the sum of the contents of $C_{16}H_{19}N_3O_4S$, $C_{16}H_{17}N_3O_4S$ and $C_{16}H_{21}N_3O_4S$. Calculate the content of $C_{16}H_{19}N_3O_4S$ (cefradine) using the declared content of $C_{16}H_{19}N_3O_4S$ in *cefradine BPCRS*. Calculate the content of $C_{16}H_{17}N_3O_4S$ (cefalexin) using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS*. Calculate the content of $C_{16}H_{21}N_3O_4S$ (4′,5′-dihydrocefradine) using the declared content of $C_{16}H_{17}N_3O_4S$ in *cefalexin BPCRS* and multiplying the area of the peak due to 4′,5′-dihydrocefradine by a correction factor of 1.6.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The Oral Suspension should be stored at the temperature and used within the period stated on the label.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Cefradine.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ceftazidime Eye Drops

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Cephalosporin antibacterial.

DEFINITION

Ceftazidime Eye Drops are a sterile solution of Ceftazidime Pentahydrate and Sodium Carbonate in a suitable vehicle.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of ceftazidime, $C_{22}H_{22}N_6O_7S_2$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless or pale yellow solution.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

B. Yields reaction A characteristic of *carbonates* and reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH, 6.0 to 8.0, Appendix V L.

Pyridine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) Dilute a volume of the eye drops, if necessary, to produce a solution containing the equivalent of 0.5% w/v of ceftazidime in a mixture of 1 volume of *acetonitrile* and 40 volumes of mobile phase A.

(2) 0.00025% w/v of *pyridine* in mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS 2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 3.6 g of *disodium hydrogen orthophosphate* and 1.4 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust the pH to 3.4 with a 10% v/v solution of *orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	96→89	4→11	linear gradient
4-7	89	11	isocratic
7-10	89→84	11→16	linear gradient
10-13	84→80	16→20	linear gradient
13-17	80→50	20→50	linear gradient
17-20	50→20	50→80	linear gradient
20-24	20	80	isocratic
24-25	20→96	80→4	linear gradient
25-33	96	4→11	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time of ceftazidime is about 8 minutes and the retention of pyridine relative to ceftazidime is about 0.4.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to pyridine is not greater than 10 times the area of the peak due to pyridine in the chromatogram obtained with solution (2) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *acetonitrile* and 20 volumes of mobile phase A, protected from light.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dilute a volume of the eye drops, if necessary, to produce a solution containing the equivalent of 0.1% w/v of ceftazidime.

(2) Dilute 3 volumes of solution (1) to 50 volumes and further dilute 1 volume to 20 volumes.

(3) Heat 20 mL of a 0.1% w/v solution of *ceftazidime EPCRS* at 80° for 15 minutes (generation of impurity A).

(4) Dilute 2 volumes of solution (2) to 3 volumes.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Pyridine may be used, but using an injection volume of 5 µL.

When the chromatograms are recorded under the prescribed conditions the retention time of ceftazidime is about 8 minutes. The retentions relative to ceftazidime are: impurity A, about 0.9; impurity B, about 1.4; impurity F (pyridine), about 0.4; impurity G, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and ceftazidime is at least 2.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity G and multiply the area of any such peak by the following correction factor: 3.0.

In the chromatogram obtained with solution (1):

the areas of any peaks corresponding to impurities A and B are not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.3% of each);

the area of any peak corresponding to impurity G is not greater than 3.3 times the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (4) (0.05%) and any peak due to pyridine (impurity F).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *acetonitrile* and 20 volumes of mobile phase A, protected from light.

(1) Dilute a volume of the eye drops, if necessary, to produce a solution containing the equivalent of 0.1% w/v of ceftazidime.

(2) 0.1% w/v of *ceftazidime EPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuvienthuocngocanh.com/

The chromatographic conditions described under Pyridine may be used, but using an injection volume of 5 µL.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{22}N_6O_7S_2$ in the eye drops using the declared content of $C_{22}H_{22}N_6O_7S_2$ in *ceftazidime EPCRS*.

STORAGE

Ceftazidime Eye Drops should be protected from light and stored at a temperature not exceeding -20°. When thawed, Ceftazidime Eye Drops should be stored at a temperature of 2° to 8° and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ceftazidime.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ceftazidime Pentahydrate and under Ceftazidime Pentahydrate with Sodium Carbonate for Injection.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ceftazidime for Injection

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Ceftazidime for Injection is a sterile mixture of Ceftazidime Pentahydrate and Sodium Carbonate. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of ceftazidime, $C_{22}H_{22}N_6O_7S_2$

90.0 to 110.0% of the stated amount.

Content of sodium carbonate, Na_2CO_3

8.0 to 10.0% w/w.

CHARACTERISTICS

White or slightly yellow powder.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

B. Yields reaction A characteristic of *carbonates* and reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 10% w/v of ceftazidime, 5.0 to 7.5, Appendix V L.

Clarity of solution

A solution containing the equivalent of 10% w/v of ceftazidime in *carbon dioxide-free water* is *clear*, Appendix IV A.

Pyridine

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Disperse a quantity of the contents of a sealed container containing the equivalent of 0.5 g of ceftazidime in 10 mL of a 10% v/v solution of *phosphate buffer solution pH 7.0 R4* and add sufficient of the same buffer solution to produce 100 mL.
(2) To 1 volume of a solution containing 0.025% w/v of *pyridine* in *water*, add 10 volumes of *phosphate buffer solution pH 7.0 R4* and dilute to 100 volumes with *water*.
(3) Dilute 1 volume of solution (1) to 200 volumes with a 10% v/v solution of *phosphate buffer solution pH 7.0 R4*. To 1 volume of this solution add 20 volumes of solution (2) and dilute to 200 volumes with a 10% v/v solution of *phosphate buffer solution pH 7.0 R4*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb S5 ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 255 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

8 volumes of a 2.88% w/v solution of *ammonium dihydrogen orthophosphate*, previously adjusted to pH 7.0 with *ammonia*, 24 volumes of *acetonitrile* and 68 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ceftazidime and pyridine is at least 7.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to pyridine is not greater than 10 times the area of the peak due to pyridine in the chromatogram obtained with solution (2) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the contents of a sealed container containing the equivalent of 0.15 g of ceftazidime in 5 mL of *acetonitrile*, dissolve by adding *water* and add sufficient *water* to produce 100 mL.
(2) To 1 volume of solution (1) add 5 volumes of *acetonitrile* and add sufficient *water* to produce 100 volumes. Dilute 1 volume of this solution to 5 volumes with *water*.
(3) Expose 5 mL of solution (1) to *ultraviolet light (254 nm)* for 24 hours (generation of impurity B).
(4) Disperse 3 mg of *ceftazidime for peak identification EPCRS* (containing impurities A and G) in 0.5 mL of *acetonitrile*, dissolve by adding *water* and add sufficient *water* to produce 2 mL.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Bakerbond BDC and Inertsil ODS 3 are suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 3.6 g of *disodium hydrogen orthophosphate* and 1.4 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust the pH to 3.4 with a 10% v/v solution of *orthophosphoric acid*.

Mobile phase B *acetonitrile* for chromatography.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 4	96 → 89	4 → 11	linear gradient
4 - 5	89	11	isocratic
5 - 8	89 → 84	11 → 16	linear gradient
8 - 11	84 → 80	16 → 20	linear gradient
11 - 15	80 → 50	20 → 50	linear gradient
15 - 18	50 → 20	50 → 80	linear gradient
18 - 22	20	80	isocratic

When the chromatograms are recorded under the prescribed conditions the retention times relative to ceftazidime (retention time, about 8 minutes) are: impurity F, about 0.4; impurity G, about 0.8; impurity A, about 0.9; impurity B, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity A and ceftazidime is at least 4.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B and G using the chromatograms obtained with solutions (3) and (4) and the chromatogram supplied with *ceftazidime for peak identification EPCRS*. Multiply the area of any peak corresponding to impurity G by the following correction factor: 3.0.

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity A, B or G is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2% for each);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any such peaks is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%) and any peak due to impurity F (pyridine).

Loss on drying

When dried *in vacuo* at 25° at a pressure not exceeding 0.67 kPa for 4 hours, lose not more than 13.5% of their weight. Use 0.3 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg per mL of ceftazidime (solution A). The endotoxin limit concentration of solution A is 1.0 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

For ceftazidime

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the mixed contents of the 10 containers containing the equivalent of 0.1 g of ceftazidime in 10 mL of the mobile phase and add sufficient mobile phase to produce 100 mL.
(2) 0.1% w/v of *ceftazidime EPCRS* in the mobile phase.
(3) 0.1% w/v of *ceftazidime for peak identification EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *hexylsilyl silica gel for chromatography* (5 µm) (Spherisorb hexyl is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 245 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

2 volumes of *acetonitrile* and 98 volumes of a solution containing equal volumes of 0.43% w/v of *disodium hydrogen orthophosphate* and 0.27% w/v of *potassium dihydrogen orthophosphate*.

When the chromatograms are recorded under the prescribed conditions the retention time of ceftazidime is about 4.5 minutes and the retention time of impurity A relative to that of ceftazidime is about 0.7.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and ceftazidime is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{22}N_6O_7S_2$ in a container of average content weight from the chromatograms obtained and from the declared content of $C_{22}H_{22}N_6O_7S_2$ in *ceftazidime EPCRS*.

For sodium carbonate

Carry out the method for *atomic absorption spectrophotometry*, Appendix II D, using the following solutions.

Test solution Dissolve a quantity of the mixed contents of the 10 containers in sufficient *water* to produce a solution containing the equivalent of 0.65% w/v of ceftazidime. To 10 mL of this solution add 5 mL of a caesium chloride buffer solution, prepared by adding 500 mL of *water* and 86 mL of *hydrochloric acid* to 12.7 g of *caesium chloride* and diluting to 1000 mL with *water*; dilute this solution to 50 mL with *water*.

Reference solution Transfer 20 mL of the caesium chloride buffer solution into each of 4 identical flasks. Add 0 mL, 5 mL, 10 mL and 15 mL, respectively, of a sodium standard solution (containing 1000 mg per litre) into the flasks and add sufficient *water* to produce 200 mL. To prepare the sodium standard solution dissolve 3.7 g of *sodium nitrate* in *water* and add sufficient *water* to produce 500 mL; add 48.5 g of *nitric acid* and dilute to 1000 mL with *water*.

Measure the absorbance at 330 nm using a sodium hollow-cathode lamp and an air-acetylene flame. Each mg of sodium is equivalent to 4.6087 mg of Na_2CO_3.

STORAGE

The sealed container should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ceftazidime.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ceftazidime Pentahydrate and under Ceftazidime Pentahydrate with Sodium Carbonate for Injection.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ceftazidime Injection

General Notices

Ceftazidime Infusion

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Cephalosporin antibacterial.

DEFINITION

Ceftazidime Injection is a sterile solution containing Ceftazidime Pentahydrate and Sodium Carbonate in a suitable diluent. It is supplied as a ready-to-use solution.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of ceftazidime, $C_{22}H_{22}N_6O_7S_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dilute a volume of the injection with a mixture containing 1 volume of 2M *hydrochloric acid* and 39 volumes of *water* to produce a solution containing the equivalent of 0.0015% w/v of ceftazidime. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits a maximum at about 260 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 8.0, Appendix V L.

Pyridine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Dilute a quantity of the injection with sufficient of a 10% v/v solution of *phosphate buffer solution pH 7.0 R4* to produce a solution containing the equivalent of 0.5% w/v of ceftazidime.

www.webofpharma.com

https://nhathuocngocanh.com/

(2) To 1 volume of a solution containing 0.025% w/v of *pyridine* in *water*, add 10 volumes of *phosphate buffer solution pH 7.0 R4* and dilute to 100 volumes with *water*.

(3) Dilute 1 volume of solution (1) to 200 volumes with a 10% v/v solution of *phosphate buffer solution pH 7.0 R4*. To 1 volume of this solution add 20 volumes of solution (2) and dilute to 200 volumes with a 10% v/v solution of *phosphate buffer solution pH 7.0 R4*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb S5 ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 255 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

8 volumes of a 2.88% w/v solution of *ammonium dihydrogen orthophosphate*, previously adjusted to pH 7.0 with *ammonia*, 24 volumes of *acetonitrile* and 68 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ceftazidime and pyridine is at least 7.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to pyridine is not greater than 10 times the area of the peak due to pyridine in the chromatogram obtained with solution (2) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection to produce a solution containing the equivalent of 0.15% w/v of ceftazidime by dispersing in 5 volumes of *acetonitrile* and then adding sufficient *water* to produce 100 volumes.

(2) To 1 volume of solution (1) add 5 volumes of *acetonitrile* and add sufficient *water* to produce 100 volumes. Dilute 1 volume of this solution to 5 volumes with *water*.

(3) Expose 5 mL of solution (1) to *ultraviolet light (254 nm)* for 24 hours (generation of impurity B).

(4) Disperse 3 mg of *ceftazidime for peak identification EPCRS* (containing impurities A and G) in 0.5 mL of *acetonitrile*, dissolve by adding *water* and add sufficient *water* to produce 2 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Bakerbond BDC and Inertsil ODS 3 are suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.3 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 3.6 g of *disodium hydrogen orthophosphate* and 1.4 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust the pH to 3.4 with a 10% v/v solution of *orthophosphoric acid*.

Mobile phase B *acetonitrile for chromatography*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	96→89	4→11	linear gradient
4-5	89	11	isocratic
5-8	89→84	11→16	linear gradient
8-11	84→80	16→20	linear gradient
11-15	80→50	20→50	linear gradient
15-18	50→20	50→80	linear gradient
18-22	20	80	isocratic

When the chromatograms are recorded under the prescribed conditions the retention times relative to ceftazidime (retention time, about 8 minutes) are: impurity F, about 0.4; impurity G, about 0.8; impurity A, about 0.9; impurity B, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity A and ceftazidime is at least 4.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B and G using the chromatograms obtained with solutions (3) and (4) and the chromatogram supplied with *ceftazidime for peak identification EPCRS*. Multiply the area of any peak corresponding to impurity G by the following correction factor: 3.0.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A or B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2% of each);

the area of any peak corresponding to impurity G is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%) and any peak due to impurity F (pyridine).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, with *water BET* to give a solution containing the equivalent of 10 mg per mL of ceftazidime (solution A). The endotoxin limit concentration of solution A is 1.0 IU per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection with sufficient of the mobile phase to produce a solution containing the equivalent of 0.1% w/v of ceftazidime.
(2) 0.1% w/v of *ceftazidime EPCRS* in the mobile phase.
(3) 0.1% w/v of *ceftazidime for peak identification EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *hexylsilyl silica gel for chromatography* (5 µm) (Spherisorb hexyl is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 245 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of *acetonitrile* and 98 volumes of a solution containing equal volumes of 0.43% w/v *disodium hydrogen orthophosphate* and 0.27% w/v *potassium dihydrogen orthophosphate*.

When the chromatograms are recorded under the prescribed conditions the retention time of ceftazidime is about 4.5 minutes and the retention of impurity A relative to that of ceftazidime is about 0.7.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and ceftazidime is at least 1.5.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuathuocngocanh.com/

Calculate the content of $C_{22}H_{22}N_6O_7S_2$ in the injection from the chromatograms obtained and from the declared content of $C_{22}H_{22}N_6O_7S_2$ in *ceftazidime EPCRS*.

STORAGE

Ceftazidime Injection should be stored at a temperature of 2° to 8°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ceftazidime.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Ceftazidime Pentahydrate and under Ceftazidime Pentahydrate with Sodium Carbonate for Injection.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuvienthuocngocanh.com/

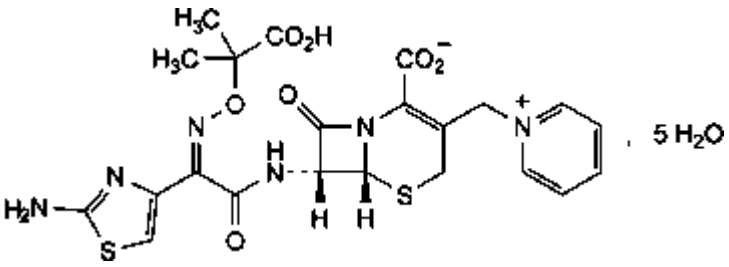
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ceftazidime Pentahydrate

General Notices

Ceftazidime

(Ph. Eur. monograph 1405)



$C_{22}H_{22}N_6O_7S_2,5H_2O$ 637 *78439-06-2*

Action and use

Cephalosporin antibacterial.

Preparations

Ceftazidime Eye Drops

Ceftazidime for Injection

Ceftazidime Injection

Ph Eur

DEFINITION

(6*R*,7*R*)-7-[[(2*Z*)-2-(2-Aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, crystalline powder.

Solubility

Slightly soluble in water and in methanol, practically insoluble in acetone and in ethanol (96 per cent). It dissolves in acid and alkali solutions.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *ceftazidime CRS*.

TESTS

Solution S

Dissolve 0.25 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

3.0 to 4.0 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Suspend 0.150 g of the substance to be examined in 5 mL of *acetonitrile R*, dissolve by adding *water R* and dilute to 100 mL with *water R*.

Reference solution (a) To 1.0 mL of the test solution add 5.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 5.0 mL with *water R*.

Reference solution (b) In order to prepare impurity B *in situ*, expose 5 mL of the test solution to ultraviolet light at 254 nm for about 24 h.

Reference solution (c) Dissolve the contents of a vial of *ceftazidime for peak identification CRS* (containing impurities A and G) in 2.0 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: solution containing 3.6 g/L of *disodium hydrogen phosphate dodecahydrate R* and 1.4 g/L of *potassium dihydrogen phosphate R*, adjusted to pH 3.4 with a 10 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	96 → 89	4 → 11
4 - 5	89	11
5 - 8	89 → 84	11 → 16
8 - 11	84 → 80	16 → 20
11 - 15	80 → 50	20 → 50
15 - 18	50 → 20	50 → 80
18 - 22	20	80

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Relative retention With reference to ceftazidime (retention time = about 8 min): impurity F = about 0.4; impurity G = about 0.8; impurity A = about 0.9; impurity B = about 1.4.

Identification of impurities Use the chromatogram supplied with *ceftazidime for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and G; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to impurity A and ceftazidime.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 3.0;

— *impurities A, B, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to impurity F.

Impurity F

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Phosphate buffer solution Prepare a 10 per cent *V/V* solution of *phosphate buffer solution pH 7.0 R4*.

Test solution Dissolve 0.500 g of the substance to be examined in phosphate buffer solution and dilute to 100.0 mL with the same solution.

Reference solution (a) Dissolve 1.00 g of *pyridine R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 200.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with phosphate buffer solution.

Reference solution (b) Dilute 1 mL of the test solution to 200 mL with phosphate buffer solution. To 1 mL of this solution add 20 mL of reference solution (a) and dilute to 200 mL with phosphate buffer solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 8 volumes of a 28.8 g/L solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 7.0 with *ammonia R*, 24 volumes of *acetonitrile R* and 68 volumes of *water R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 255 nm.

Injection 20 µL.

Run time 10 min.

System suitability Reference solution (b):

— *resolution*: minimum 7.0 between the peaks due to ceftazidime and impurity F.

Limit:

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (500 ppm).

Water (2.5.12)

13.0 per cent to 15.0 per cent, determined on 0.100 g.

Bacterial endotoxins (2.6.14)

www.webofpharma.com

https://thuocngocanh.com/

Less than 0.10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *ceftazidime CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *ceftazidime for peak identification CRS* (containing impurities A and G) in 3.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *hexylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 4.3 g of *disodium hydrogen phosphate dodecahydrate R* and 2.7 g of *potassium dihydrogen phosphate R* in 980 mL of *water R*, then add 20 mL of *acetonitrile R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 245 nm.

Injection 20 µL.

Run time 6 min.

Relative retention With reference to ceftazidime (retention time = about 4.5 min): impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity A and ceftazidime.

Calculate the content of ceftazidime ($C_{22}H_{22}N_6O_7S_2$) taking into account the assigned content of $C_{22}H_{22}N_6O_7S_2$ in *ceftazidime CRS*.

STORAGE

In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

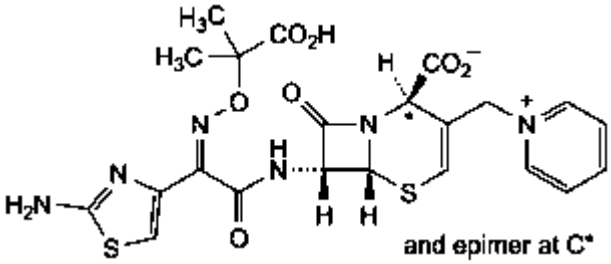
IMPURITIES

Specified impurities *A, B, F, G.*

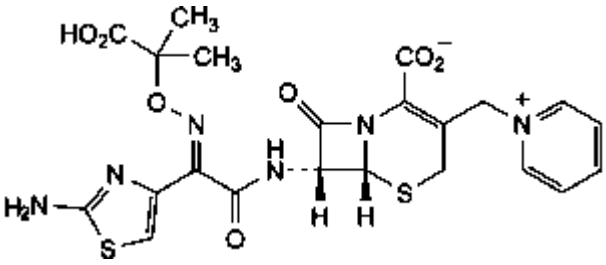
www.webofpharma.com

https://thuvienthuocngocanh.com/

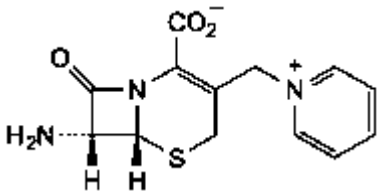
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, H.*



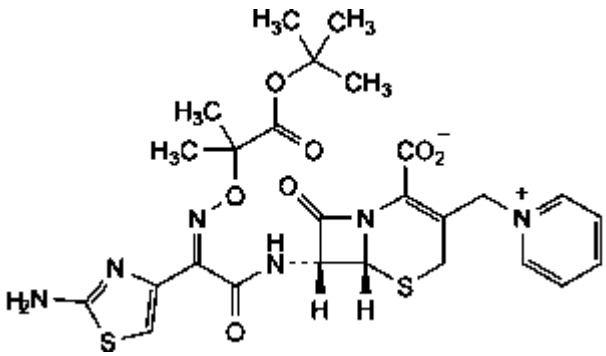
A. (2*RS*,6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (Δ-2-ceftazidime),



B. (6*R*,7*R*)-7-[[(2*E*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



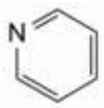
C. (6*R*,7*R*)-7-amino-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



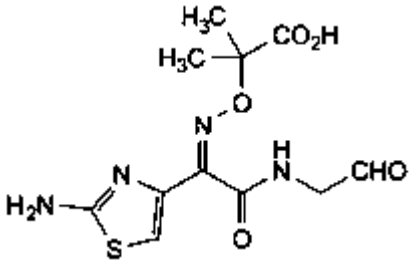
E. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

www.webofpharma.com

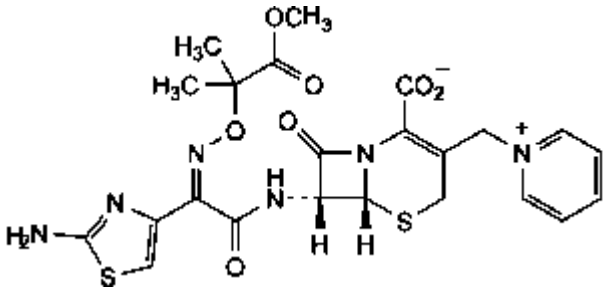
https://thuvienthuocngocanh.com/



F. pyridine,



G. 2-[[[(1*Z*)-1-(2-aminothiazol-4-yl)-2-[(oxoethyl)amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoic acid,



H. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(2-methoxy-1,1-dimethyl-2-oxoethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ceftazidime Pentahydrate with Sodium Carbonate for Injection

General Notices

(Ph. Eur. monograph 2344)

Action and use

Cephalosporin antibacterial.

Preparations

Ceftazidime Eye Drops

Ceftazidime for Injection

Ceftazidime Injection

Ph Eur

DEFINITION

Sterile mixture of *Ceftazidime pentahydrate (1405)* and *Anhydrous sodium carbonate (0773)*.

Semi-synthetic product derived from a fermentation product.

Content

— *ceftazidime*: 93.0 per cent to 105.0 per cent (dried and carbonate-free substance);

— *sodium carbonate*: 8.0 per cent to 10.0 per cent.

CHARACTERS

Appearance

White or pale yellow powder.

Solubility

Freely soluble in water and in methanol, practically insoluble in acetone.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

www.webofpharma.com

https://thuocngocanh.com/

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. It gives the reaction of carbonates (2.3.1).

TESTS

Solution S

Dissolve 2.60 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and its absorbance (2.2.25) at 425 nm is not greater than 0.50.

pH (2.2.3)

5.0 to 7.5 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Suspend 0.150 g of the substance to be examined in 5 mL of *acetonitrile R*, dissolve by adding *water R* and dilute to 100 mL with *water R*.

Reference solution (a) To 1.0 mL of the test solution add 5.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 5.0 mL with *water R*.

Reference solution (b) In order to prepare impurity B *in situ*, expose 5 mL of the test solution to ultraviolet light at 254 nm for about 24 h.

Reference solution (c) Dissolve the contents of a vial of *ceftazidime for peak identification CRS* (containing impurities A and G) in 2.0 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: solution containing 3.6 g/L of *disodium hydrogen phosphate dodecahydrate R* and 1.4 g/L of *potassium dihydrogen phosphate R*, adjusted to pH 3.4 with a 10 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	96 → 89	4 → 11
4 - 5	89	11
5 - 8	89 → 84	11 → 16
8 - 11	84 → 80	16 → 20
11 - 15	80 → 50	20 → 50
15 - 18	50 → 20	50 → 80
18 - 22	20	80

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Relative retention With reference to ceftazidime (retention time = about 8 min): impurity F = about 0.4; impurity G = about 0.8; impurity A = about 0.9; impurity B = about 1.4.

Identification of impurities Use the chromatogram supplied with *ceftazidime for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and G; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to impurity A and ceftazidime.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 3.0;

— *impurities A, B, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to impurity F.

Impurity F

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Phosphate buffer solution Prepare a 10 per cent *V*/*V* solution of *phosphate buffer solution pH 7.0 R4*.

Test solution Dissolve 0.500 g of the substance to be examined in phosphate buffer solution and dilute to 100.0 mL with the same solution.

Reference solution (a) Dissolve 1.00 g of *pyridine R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 200.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with phosphate buffer solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 200.0 mL with phosphate buffer solution. To 1.0 mL of this solution add 20.0 mL of reference solution (a) and dilute to 200.0 mL with phosphate buffer solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 8 volumes of a 28.8 g/L solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 7.0 with *ammonia R*, 24 volumes of *acetonitrile R* and 68 volumes of *water R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 255 nm.

Injection 20 µL.

Run time 10 min.

System suitability Reference solution (b):

— *resolution*: minimum 7.0 between the peaks due to ceftazidime and impurity F.

Limit:

— *impurity F*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent).

Loss on drying (2.2.32)

Maximum 13.5 per cent, determined on 0.300 g. Dry at 25 °C at a pressure not exceeding 0.67 kPa for 4 h then heat the residue at 100 °C at a pressure not exceeding 0.67 kPa for 3 h.

Bacterial endotoxins (2.6.14)

Less than 0.10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Ceftazidime

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of ceftazidime CRS in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of ceftazidime for peak identification CRS (containing impurities A and G) in 3.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: hexylsilyl silica gel for chromatography R (5 µm).

Mobile phase Dissolve 4.3 g of disodium hydrogen phosphate dodecahydrate R and 2.7 g of potassium dihydrogen phosphate R in 980 mL of water R, then add 20 mL of acetonitrile R.

Flow rate 2 mL/min.

Detection Spectrophotometer at 245 nm.

Injection 20 µL.

Run time 6 min.

Relative retention With reference to ceftazidime (retention time = about 4.5 min): impurity A = about 0.7.

System suitability Reference solution (b):

— resolution: minimum 1.5 between the peaks due to impurity A and ceftazidime.

Calculate the content of ceftazidime ($C_{22}H_{22}N_6O_7S_2$) taking into account the assigned content of $C_{22}H_{22}N_6O_7S_2$ in ceftazidime CRS.

Sodium carbonate

Atomic absorption spectrometry (2.2.23, Method I).

Caesium chloride buffer solution To 12.7 g of caesium chloride R add 500 mL of water R and 86 mL of hydrochloric acid R and dilute to 1000.0 mL with water R.

Sodium standard solution (1000 mg/L) Dissolve 3.70 g of sodium nitrate R in water R and dilute to 500 mL with the same solvent, add 48.5 g of nitric acid R and dilute to 1000 mL with water R.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Test solution Dissolve 650.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent. To 10.0 mL of this solution add 5.0 mL of caesium chloride buffer solution and dilute to 50.0 mL with *water R*.

Reference solution Into 4 identical flasks, each containing 20.0 mL of caesium chloride buffer solution, introduce respectively 0 mL, 5.00 mL, 10.00 mL and 15.00 mL of sodium standard solution (1000 mg/L) and dilute to 200.0 mL with *water R*.

Source Sodium hollow-cathode lamp.

Wavelength 330.2 nm to 330.3 nm.

Atomisation device Air-acetylene flame.

Calculate the percentage content of sodium carbonate.

STORAGE

In a sterile, airtight, tamper-evident container, protected from light and humidity.

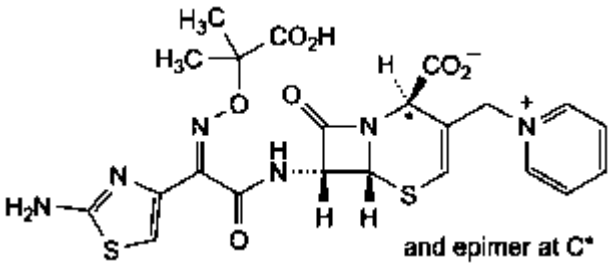
LABELLING

The label states the percentage content *m/m* of ceftazidime.

IMPURITIES

Specified impurities *A, B, F, G.*

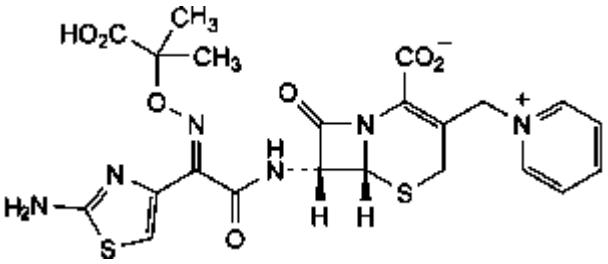
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, H.*



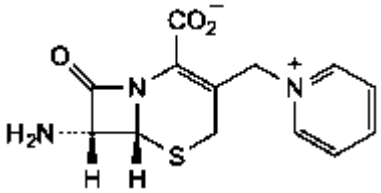
A. (2*RS*,6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (Δ-2-ceftazidime),

www.webofpharma.com

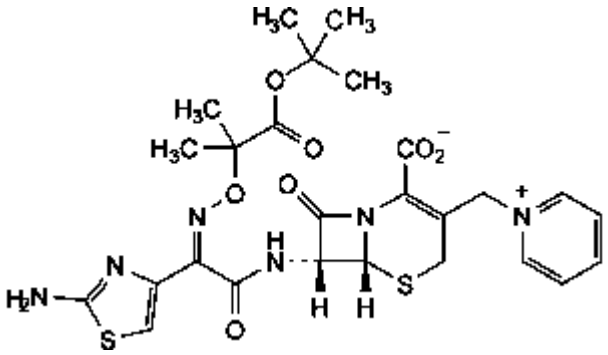
https://thuocngocanh.com/



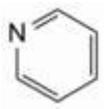
B. (6*R*,7*R*)-7-[[(2*E*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



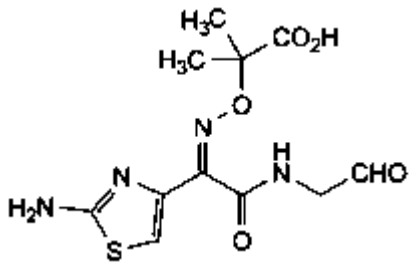
C. (6*R*,7*R*)-7-amino-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



E. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



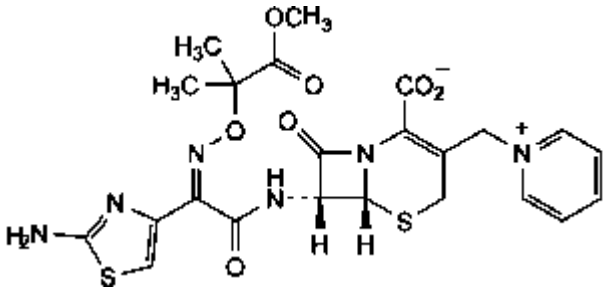
F. pyridine,



G. 2-[[[(1*Z*)-1-(2-aminothiazol-4-yl)-2-[(oxoethyl)amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoic acid,

www.webofpharma.com

https://thuvienthuocngocanh.com/



H. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(2-methoxy-1,1-dimethyl-2-oxoethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ceftriaxone Injection

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Ceftriaxone Injection is a sterile solution of Ceftriaxone Sodium in Water for Injections. It is prepared by dissolving Ceftriaxone Sodium for Injection in the requisite amount of Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Ceftriaxone Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

CEFTRIAXONE SODIUM FOR INJECTION

DEFINITION

Ceftriaxone Sodium for Injection is a sterile material prepared from Ceftriaxone Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of ceftriaxone, $C_{18}H_{18}N_8O_7S_3$

92.0 to 108.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of ceftriaxone sodium *(RS 046)*.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

C. Yield reaction A characteristic *of sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

www.webofpharma.com

https://thuocngocanh.com/

Acidity or alkalinity

pH of a solution containing the equivalent of 12.0% w/v of ceftriaxone, 6.0 to 8.0, Appendix V L.

Clarity and colour of solution

A solution containing the equivalent of 1.20% w/v of ceftriaxone in *carbon dioxide-free water* is *clear,* Appendix IV A, and not more intensely coloured than *reference solution* Y_5 or BY_5, Appendix IV B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a quantity of the mixed contents of the 10 containers to produce a solution containing the equivalent of 0.030% w/v of ceftriaxone.
(2) 0.0050% w/v each of *ceftriaxone sodium BPCRS* and *ceftriaxone impurity A EPCRS*.
(3) Dilute 1 volume of solution (1) to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP-18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of solutions (1), (3) and (4).
(g) Allow the chromatography to proceed for twice the retention time of the peak due to ceftriaxone sodium.

MOBILE PHASE

Dissolve 2 g of *tetradecylammonium bromide* and 2 g of *tetraheptylammonium bromide* in a mixture of 440 mL of *water*, 55 mL of 0.067M *mixed phosphate buffer pH 7.0*, 5 mL of a citrate buffer solution pH 5.0 prepared by dissolving 20.17 g of *citric acid* in 800 mL of *water*, adjusting to pH 5.0 with 10M *sodium hydroxide* and diluting to 1000 mL with *water*, and 500 mL of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to ceftriaxone sodium and ceftriaxone sodium *E*-isomer is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the sum of the areas of all the *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (3) (5%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

www.webofpharma.com

https://thuvienthuocngocanh.com/

Water

Not more than 11.0% w/w, Appendix IX C, Method I. Use 0.1 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of ceftriaxone per mL (solution A). The endotoxin limit concentration of solution A is 0.8 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a quantity of the mixed contents of the 10 containers to produce a solution containing the equivalent of 0.030% w/v of ceftriaxone.
(2) 0.030% w/v of *ceftriaxone sodium BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{18}N_8O_7S_3$ in a container of average content weight from the declared content of $C_{18}H_{16}N_8Na_2O_7S_3$ in *ceftriaxone sodium BPCRS*.

STORAGE

The sealed container should be stored at a temperature not exceeding 30°.

LABELLING

The label of the sealed container states the quantity of Ceftriaxone Sodium contained in it in terms of the equivalent amount of ceftriaxone.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

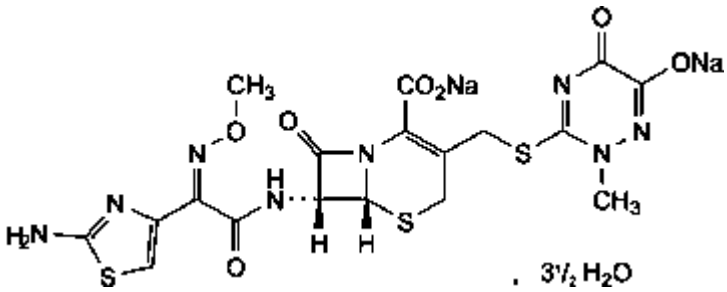
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ceftriaxone Sodium

General Notices

(Ph. Eur. monograph 0991)



$C_{18}H_{16}N_8Na_2O_7S_3,3½H_2O$ 662 *104376-79-6*

Action and use

Cephalosporin antibacterial.

Preparation

Ceftriaxone Injection

Ph Eur

DEFINITION

Disodium (6*R*,7*R*)-7-[[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 3.5 hydrate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Almost white or yellowish, slightly hygroscopic, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, sparingly soluble in methanol, very slightly soluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *ceftriaxone sodium CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 2.40 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 or BY_5 (*2.2.2*).

Dilute 2 mL of solution S to 20 mL with *water R*.

pH (*2.2.3*)

6.0 to 8.0 for solution S.

Specific optical rotation (*2.2.7*)

-155 to -170 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 30.0 mg of *ceftriaxone sodium CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *ceftriaxone sodium CRS* and 5.0 mg of *ceftriaxone impurity A CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

www.webofpharma.com

https://nhathuocngocanh.com/

Mobile phase Dissolve 2.0 g of *tetradecylammonium bromide R* and 2.0 g of *tetraheptylammonium bromide R* in a mixture of 440 mL of *water R*, 55 mL of *0.067 M phosphate buffer solution pH 7.0 R*, 5.0 mL of citrate buffer solution pH 5.0 prepared by dissolving 20.17 g of *citric acid monohydrate R* in 800 mL of *water R*, adjusting to pH 5.0 with *strong sodium hydroxide solution R* and diluting to 1000.0 mL with *water R*, and 500 mL of *acetonitrile R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of ceftriaxone.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to ceftriaxone and impurity A.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (4.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.8 per cent *m/m*.

Water (*2.5.12*)

8.0 per cent to 11.0 per cent, determined on 0.100 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.08 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{18}H_{16}N_8Na_2O_7S_3$ from the declared content of *ceftriaxone sodium CRS*.

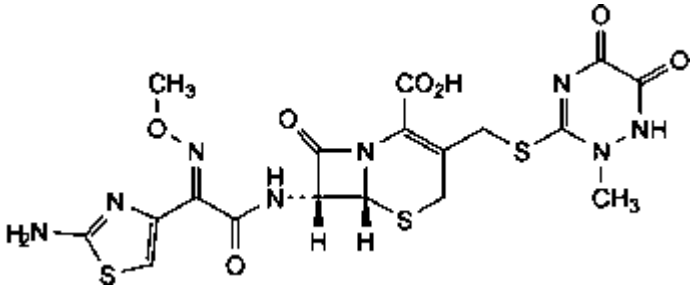
www.webofpharma.com

https://thuocngocanh.com/

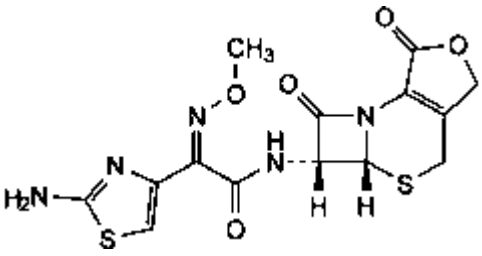
STORAGE

In an airtight container protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

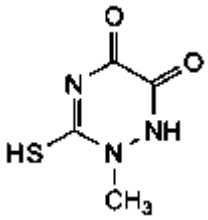
IMPURITIES



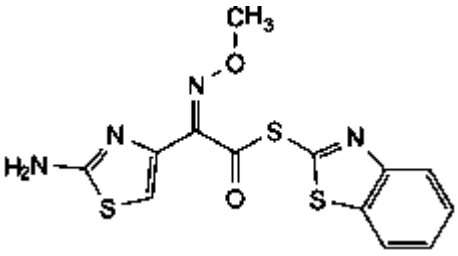
A. (6*R*,7*R*)-7-[[(2*E*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (*(E)*-isomer),



B. (5a*R*,6*R*)-6-[[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione,



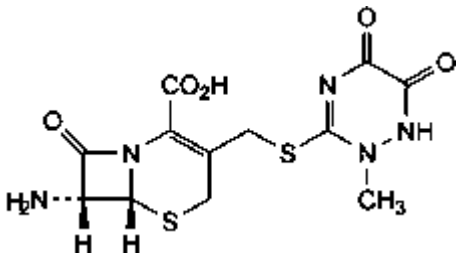
C. 2-methyl-3-sulfanyl-1,2-dihydro-1,2,4-triazine-5,6-dione,



D. *S*-benzothiazol-2-yl (2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)thioacetate,

www.webofpharma.com

https://thuocngocanh.com/



E. (6*R*,7*R*)-7-amino-3-[[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

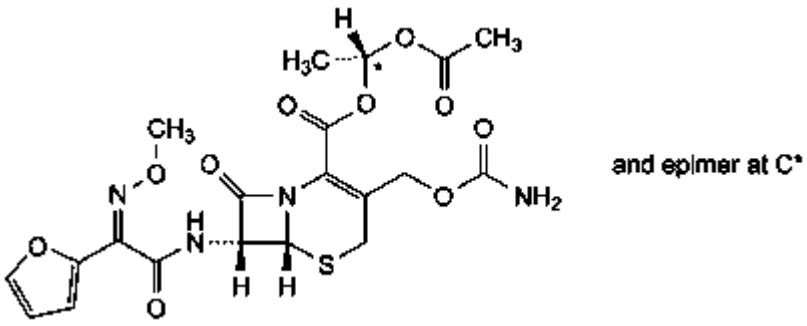
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefuroxime Axetil

General Notices

(Ph. Eur. monograph 1300)



$C_{20}H_{22}N_4O_{10}S$ 510.5 *64544-07-6*

Action and use

Cephalosporin antibacterial.

Preparations

Cefuroxime Axetil Oral Suspension

Cefuroxime Axetil Tablets

Ph Eur

DEFINITION

Mixture of the 2 diastereoisomers of (1*RS*)-1-(acetyloxy)ethyl (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(2*Z*)-2-(furan-2-yl)-2(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Solubility

Slightly soluble in water, soluble in acetone, in ethyl acetate and in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *cefuroxime axetil CRS*.

B. Examine the chromatograms obtained in the assay.

Results The principal peaks in the chromatogram obtained with the test solution are similar in retention time and size to the peaks due to cefuroxime axetil diastereoisomers A and B in the chromatogram obtained with reference solution (d).

TESTS

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Prepare the test solution and reference solution (d) immediately before use.*

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) In order to prepare *in situ* impurity A, heat 5 mL of the test solution at 60 °C for 1 h.

Reference solution (c) In order to prepare *in situ* impurity B, expose 5 mL of the test solution to ultraviolet light at 254 nm for 24 h.

Reference solution (d) Dissolve 10.0 mg of *cefuroxime axetil CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *trimethylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, 23 g/L solution of *ammonium dihydrogen phosphate R* (38:62 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 278 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the pair of peaks due to impurity A and use the chromatogram obtained with reference solution (c) to identify the pair of peaks due to impurity B.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to cefuroxime axetil diastereoisomer A: cefuroxime axetil diastereoisomer B = about 0.9; impurity A = about 1.2; impurity B = 1.7 and 2.1.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to cefuroxime axetil diastereoisomer A and impurity A.

Limits:

— *impurity A*: maximum 1.5 per cent for the sum of the pair of peaks;

— *impurity B*: maximum 1.0 per cent for the sum of the pair of peaks;

— *any other impurity*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 3.0 per cent;

— *disregard limit*: 0.05 times the area of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.05 per cent).

Diastereoisomer ratio

Liquid chromatography (2.2.29) as described in the test for related substances.

Limit Test solution:

— the ratio of the area of the peak due to cefuroxime axetil diastereoisomer A to the sum of the areas of the peaks due to cefuroxime axetil diastereoisomers A and B is between 0.48 and 0.55.

Acetone (2.4.24)

Maximum 1.1 per cent.

Water (2.5.12)

Maximum 1.5 per cent, determined on 0.400 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (d).

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to cefuroxime axetil diastereoisomers A and B;

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the sum of the peaks due to cefuroxime axetil diastereoisomers A and B after 6 injections.

www.webofpharma.com

https://thuocngocanh.com/

Calculate the percentage content of $C_{20}H_{22}N_4O_{10}S$ from the sum of the areas of the 2 diastereoisomer peaks and the declared content of $C_{20}H_{22}N_4O_{10}S$ in *cefuroxime axetil CRS*.

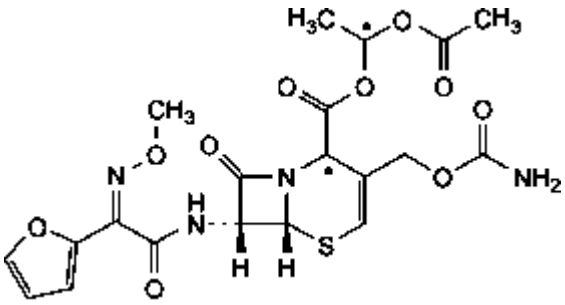
STORAGE

In an airtight container, protected from light.

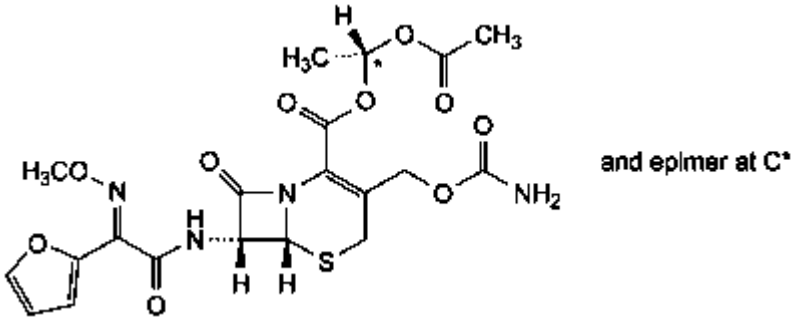
IMPURITIES

Specified impurities A, B.

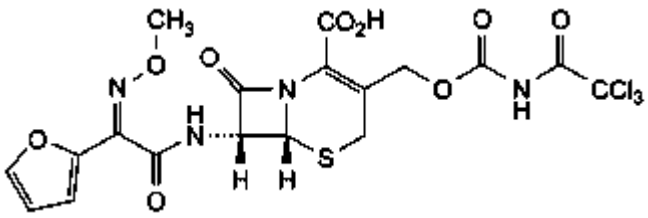
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E.



A. 1-(acetyloxy)ethyl (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(2*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (Δ^3-isomers),



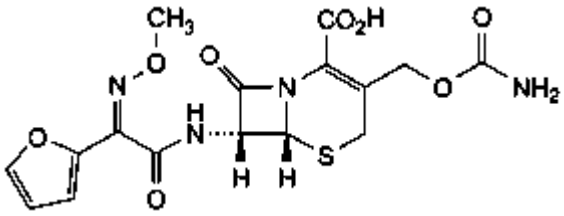
B. (1*RS*)-1-(acetyloxy)ethyl (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(2*E*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2carboxylate ((*E*)-isomers),



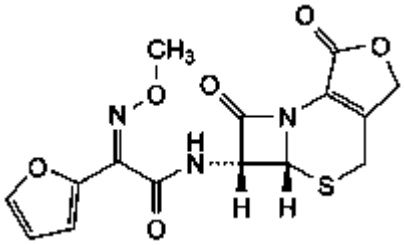
www.webofpharma.com

https://thuocngocanh.com/

C. (6*R*,7*R*)-7-[[(2*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-3-[[[(trichloroacetyl)carbamoyl]oxy]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



D. cefuroxime,



E. (5a*R*,6*R*)-6-[[(2*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione (descarbamoylcefuroxime lactone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefuroxime Axetil Oral Suspension

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefuroxime Axetil Oral Suspension is a suspension of Cefuroxime Axetil in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of Water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of cefuroxime, $C_{16}H_{16}N_4O_8S$

When freshly constituted not more than 110.0% of the stated amount. When stored at the temperature and for the period stated on the label during which the Oral Suspension may be expected to be satisfactory for use, not less than 90.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the oral suspension with sufficient *methanol* to produce a solution containing the equivalent of 0.00131% w/v of cefuroxime. The *light absorption* of the solution, Appendix II B, in the range 230 to 320 nm exhibits a maximum at 276 nm.

B. In the Assay, the retention times of the principal peaks in the chromatogram obtained with solution (1) correspond to those of the peaks due to diastereoisomers A and B of cefuroxime axetil in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 3.5 to 7.0, Appendix V L.

Dissolution

Carry out the test for dissolution described under *dissolution test for tablets and capsules*, Appendix XII B1.

Prepare a solution containing 1.43% w/v of *disodium hydrogen orthophosphate* and 0.42% w/v of *sodium dihydrogen orthophosphate* and adjust the pH to 7.0 with 20% v/v *orthophosphoric acid* or 1M *sodium hydroxide*, as necessary (solution A).

TEST CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37°, as the medium.

PROCEDURE

(1) Shake the container containing the oral suspension being examined for 30 seconds and accurately remove a volume containing one dose at a depth of 1 cm below the meniscus. Introduce the dose to the medium in the dissolution vessel. After 30 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 282 nm, Appendix II B, using solution A in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *cefuroxime axetil BPCRS*, prepared by dissolving *cefuroxime axetil BPCRS* in 5 volumes of *methanol* and then diluting to 100 volumes with solution A, using solution A in the reference cell. The equivalent concentration of cefuroxime in the final solution should be the same as that expected for solution (1).

DETERMINATION OF CONTENT

Calculate the total content of cefuroxime, $C_{16}H_{16}N_4O_8S$, in the medium from the absorbances obtained and using the declared content of $C_{20}H_{22}N_4O_{10}S$ in *cefuroxime axetil BPCRS*. Each mg of $C_{20}H_{22}N_4O_{10}S$ is equivalent to 0.8313 mg of $C_{16}H_{16}N_4O_8S$.

LIMITS

The amount of cefuroxime released is not less than 60% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*.

(1) Shake a weighed quantity of the oral suspension with sufficient *methanol* to produce a solution containing the equivalent of 0.25% w/v of cefuroxime and mix with the aid of ultrasound for 5 minutes with occasional swirling. Allow to cool to room temperature, shake vigorously and allow to stand for 10 minutes. Dilute 10 volumes of the resulting solution to 50 volumes with *methanol (23%)* and filter through a 0.45-µm PTFE filter, discarding the first 5 mL of filtrate. The solution should be used immediately or stored in the dark at a temperature of 2° to 8° before analysis.

(2) Heat a quantity of solution (1) at 60° for 1 hour or until sufficient impurities (Δ^3-isomers) have been generated.

(3) Expose a quantity of solution (1) to *ultraviolet light (254 nm)* for 24 hours or until sufficient impurities (*E*-isomers) have been generated.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with particles of silica (5 µm) the surface of which has been modified by chemically-bonded trimethylsilyl groups (Hypersil SAS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

38 volumes of *methanol* and 62 volumes of 0.2M *ammonium dihydrogen orthophosphate*.

When the chromatograms are recorded under the prescribed conditions the retention time of cefuroxime axetil diastereoisomer A is 7 to 11 minutes. The retention times relative to cefuroxime axetil diastereoisomer A are: cefuroxime, about 0.35; cefuroxime axetil diastereoisomer B, about 0.9; cefuroxime axetil Δ^3-isomers (impurity A), about 1.2; *E*-isomers (impurity B), about 1.7 and 2.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to cefuroxime axetil diastereoisomer A and cefuroxime axetil Δ^3-isomer is at least 1.5 (if necessary, adjust the composition of the mobile phase).

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to cefuroxime is not greater that 1.0%;

the sum of the areas of the pair of peaks corresponding to the *E*-isomers in the chromatogram obtained with solution (3) is not greater than 1.5%;

the sum of the areas of any peaks corresponding to the Δ^3-isomers in the chromatogram obtained with solution (2) is not greater than 2.0%;

the area of any other *secondary peak* is not greater than 0.5%;

the sum of the areas of all the *secondary peaks* is not greater than 4.5%.

Disregard any peak with an area less than 0.05%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be used immediately or stored in the dark at a temperature of 2° to 8° before analysis.

(1) Shake a weighed quantity of the oral suspension with sufficient *methanol* to produce a solution containing the equivalent of 0.25% w/v of cefuroxime and mix with the aid of ultrasound for 5 minutes with occasional swirling. Allow to cool to room temperature, shake vigorously and allow to stand for 10 minutes. Dilute 10 volumes of the resulting solution to 50 volumes with *methanol (23%)* and filter through a 0.45-µm PTFE filter, discarding the first 5 mL of filtrate.
(2) Dilute 10 volumes of a 0.3% w/v solution of *cefuroxime axetil BPCRS* in *methanol* to 50 volumes with *methanol (23%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks corresponding to cefuroxime axetil diastereoisomers A and B is at least 1.5 (if necessary, adjust the composition of the mobile phase).

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{16}H_{16}N_4O_8S$, weight in volume, as the sum of the areas of the two peaks corresponding to diastereoisomers A and B of cefuroxime axetil using the declared content of $C_{20}H_{22}N_4O_{10}S$ in *cefuroxime axetil BPCRS*. Each mg of $C_{20}H_{22}N_4O_{10}S$ is equivalent to 0.8313 mg of $C_{16}H_{16}N_4O_8S$.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The Oral Suspension should be kept at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of cefuroxime.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Cefuroxime Axetil.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefuroxime Axetil Tablets

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefuroxime Axetil Tablets contain Cefuroxime Axetil. They may be coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of cefuroxime, $C_{16}H_{16}N_4O_8S$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing the equivalent of 0.1 g of cefuroxime with 5 mL of *dichloromethane*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of cefuroxime axetil *(RS 047)*.

B. In the Assay, the retention times of the principal peaks in the chromatogram obtained with solution (1) correspond to those of the peaks due to diastereoisomers A and B of cefuroxime axetil in the chromatogram obtained with solution (4).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using solutions (1) to (3) described under Assay.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

SYSTEM SUITABILITY

The requirements stated under Assay apply.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of the pair of peaks corresponding to the *E*-isomers in the chromatogram obtained with solution (3) is not greater than 1.5% by *normalisation*;

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any peaks corresponding to the Δ^3-isomers in the chromatogram obtained with solution (2) is not greater than 2.0% by *normalisation*;

the area of any other *secondary peak* is not greater than 1.0% by *normalisation*.

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, diluted with *0.1M hydrochloric acid* to produce a solution expected to contain the equivalent of 10 to 20 µg of cefuroxime per mL, at the maximum at 278 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a solution of *cefuroxime axetil BPCRS* in 0.1M *hydrochloric acid* containing the equivalent of 10 to 20 µg of cefuroxime per mL and using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of cefuroxime axetil, $C_{16}H_{16}N_4O_8S$, in the medium from the absorbances obtained and using the declared content of $C_{20}H_{22}N_4O_{10}S$ in *cefuroxime axetil BPCRS*. Each mg of $C_{20}H_{22}N_4O_{10}S$ is equivalent to 0.8313 mg of $C_{16}H_{16}N_4O_8S$.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be used immediately or stored in the dark at a temperature of 2° to 8° before analysis.

(1) Disperse 5 tablets in 0.2M *ammonium dihydrogen orthophosphate*, previously adjusted to pH 2.4 with *orthophosphoric acid*, using 10 mL per g of the stated content of cefuroxime. Immediately add 375 mL of *methanol* and shake vigorously for 10 minutes. Mix with the aid of ultrasound for a further 10 minutes and add sufficient *methanol* to produce 500 mL. Centrifuge a portion of the solution for at least 5 minutes at 2500 rpm and then dilute a quantity of the supernatant liquid with sufficient of the mobile phase to produce a solution containing the equivalent of 0.025% w/v of cefuroxime.

(2) Heat a quantity of solution (1) at 60° for 1 hour or until sufficient impurities (Δ^3-isomers) have been generated.

(3) Expose a quantity of solution (1) to *ultraviolet light (254 nm)* for 24 hours or until sufficient impurities (*E*-isomers) have been generated.

(4) 0.03% w/v of *cefuroxime axetil BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with particles of silica (5 µm) the surface of which has been modified by chemically-bonded trimethylsilyl groups (Hypersil SAS is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

38 volumes of *methanol* and 62 volumes of 0.2M *ammonium dihydrogen orthophosphate*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to cefuroxime axetil diastereoisomer A are approximately 0.9 for cefuroxime axetil diastereoisomer B, 1.2 for the cefuroxime axetil Δ^3-isomers and 1.7 and 2.1 for the *E*-isomers.

SYSTEM SUITABILITY

The Assay is not valid unless:

in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to cefuroxime axetil diastereoisomer A and the cefuroxime axetil Δ^3-isomer is at least 1.5 (if necessary, adjust the composition of the mobile phase);

in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to cefuroxime axetil diastereoisomers A and B is at least 1.5 (if necessary, adjust the composition of the mobile phase).

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{16}N_4O_8S$ as the sum of the areas of the two peaks corresponding to diastereoisomers A and B of cefuroxime axetil and using the declared content of $C_{20}H_{22}N_4O_{10}S$ in *cefuroxime axetil BPCRS*. Each mg of $C_{20}H_{22}N_4O_{10}S$ is equivalent to 0.8313 mg of $C_{16}H_{16}N_4O_8S$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of cefuroxime.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefuroxime Eye Drops

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefuroxime Eye Drops are a sterile solution of Cefuroxime Sodium in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of cefuroxime, $C_{16}H_{16}N_4O_8S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

B. Yield reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH, 5.5 to 8.5, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the eye drops containing the equivalent of 55 mg of cefuroxime with sufficient *water* to produce 100 mL.

(2) 0.058% w/v of *cefuroxime sodium BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak is suitable).

www.webofpharma.com

https://thuvienthuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 274 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Dissolve 1.3609 g of *potassium dihydrogen orthophosphate* and 0.7708 g of *ammonium acetate* in 160 mL of *methanol* and add sufficient *water* to produce 1000 mL.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{16}N_4O_8S$ in the eye drops using the declared content of $C_{16}H_{15}N_4NaO_8S$ in *cefuroxime sodium BPCRS*.

Each mg of $C_{16}H_{15}N_4NaO_8S$ is equivalent to 0.9508 mg of $C_{16}H_{16}N_4O_8S$.

STORAGE

Cefuroxime Eye Drops should be protected from light and stored at a temperature not exceeding -20°. When thawed, Cefuroxime Eye Drops should be stored at a temperature of 2° to 8° and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of cefuroxime.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefuroxime Injection

General Notices

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefuroxime Injection is a sterile solution or suspension of Cefuroxime Sodium in Water for Injections. It is prepared by dissolving or suspending Cefuroxime Sodium for Injection in the requisite amount of Water for Injections before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Cefuroxime Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

CEFUROXIME SODIUM FOR INJECTION

DEFINITION

Cefuroxime Sodium for Injection is a sterile material consisting of Cefuroxime Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of cefuroxime, $C_{16}H_{16}N_4O_8S$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of cefuroxime sodium *(RS 048)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a quantity of the contents of a sealed container in sufficient of a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0* (solution A) to produce a solution containing the equivalent of 0.4% w/v of cefuroxime.

(2) 0.4% w/v of *cefuroxime sodium BPCRS* in solution A.

(3) 0.4% w/v of each of *cefuroxime sodium BPCRS* and *cefoxitin sodium BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use as the coating *silanised silica gel* HF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *tetrahydrofuran* and 90 volumes of a 15.0% w/v solution of *ammonium acetate*, previously adjusted to pH 6.2 with *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. Yield reaction A characteristic *of sodium salts*, Appendix VI.

TESTS

Acidity or Alkalinity

pH of a solution containing the equivalent of 10.0% w/v of cefuroxime, 5.5 to 8.5, Appendix V L.

Clarity of solution

A solution containing the equivalent of 10.0% w/v of cefuroxime in *carbon dioxide-free water* is not more opalescent than *reference suspension II*, Appendix IV A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dissolve a quantity of the contents of a sealed container to produce a solution containing the equivalent of 0.1% w/v of cefuroxime.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Heat 20 mL of a 0.1% w/v solution of *cefuroxime sodium BPCRS* in a water bath at 60° for 10 minutes, cool and inject immediately (generation of descarbamoylcefuroxime).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with particles of silica the surface of which has been modified with chemically-bonded hexylsilyl groups (5 µm) (Spherisorb S5 C6 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 273 nm.

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for at least 3 times the retention time of the principal peak.

MOBILE PHASE

1 volume of *acetonitrile* and 99 volumes of *acetate buffer pH 3.4*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to cefuroxime and descarbamoylcefuroxime is at least 2.0. If necessary, adjust the concentration of *acetonitrile* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to descarbamoylcefuroxime (located by comparison with the chromatogram obtained with solution (3)) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Water

Not more than 3.5% w/w, Appendix IX C. Use 0.4 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 10 mg of cefuroxime per mL (solution A). The endotoxin limit concentration of solution A is 1.0 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dissolve a quantity of the mixed contents of the 10 containers to produce a solution containing the equivalent of 0.1% w/v of cefuroxime.

(2) 0.1% w/v of *cefuroxime sodium BPCRS*.

(3) Heat 20 mL of a 0.1% w/v solution of *cefuroxime sodium BPCRS* in a water bath at 60° for 10 minutes, cool and inject immediately (generation of descarbamoylcefuroxime).

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with particles of silica the surface of which has been modified with chemically-bonded hexylsilyl groups (5 µm) (Spherisorb S5 C6 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 273 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *acetonitrile* and 99 volumes of *acetate buffer pH 3.4*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to cefuroxime and descarbamoylcefuroxime is at least 2.0. If necessary, adjust the concentration of *acetonitrile* in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{16}N_4O_8S$ in a container of average content weight from the declared content of $C_{16}H_{15}N_4NaO_8S$ in *cefuroxime sodium BPCRS*. Each mg of $C_{16}H_{15}N_4NaO_8S$ is equivalent to 0.9508 mg of $C_{16}H_{16}N_4O_8S$.

STORAGE

The sealed container should be protected from light.

LABELLING

The label on the sealed container states the quantity of Cefuroxime Sodium contained in it in terms of the equivalent amount of cefuroxime.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefuroxime Intracameral Injection

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Cephalosporin antibacterial.

DEFINITION

Cefuroxime Intracameral Injection is a sterile solution containing Cefuroxime Sodium in a suitable diluent. It is supplied as a ready-to-use solution.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of cefuroxime, $C_{16}H_{16}N_4O_8S$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Complies with the test for Osmolality.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of equal volumes of *methanol* and 0.067M *mixed phosphate buffer pH 7.0* (solution A).

(1) Dilute a quantity of the injection in sufficient of solution A to produce a solution containing the equivalent of 0.4% w/v of cefuroxime.

(2) 0.4% w/v of *cefuroxime sodium BPCRS* in solution A.

(3) 0.4% w/v of each of *cefuroxime sodium BPCRS* and *cefoxitin sodium BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silanised silica gel* HF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in a current of warm air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *tetrahydrofuran* and 90 volumes of a 15.0% w/v solution of *ammonium acetate*, previously adjusted to pH 6.2 with *glacial acetic acid*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 10.0% w/v of cefuroxime, 5.5 to 8.5, Appendix V L.

Clarity of solution

A solution containing the equivalent of 10.0% w/v of cefuroxime in *carbon dioxide-free water* is not more opalescent than *reference suspension II*, Appendix IV A.

Osmolality

The osmolality of the injection is 240 to 380 mosmol/kg, Appendix V N.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*. Prepare the solutions immediately before use or store at 2° to 8°.

(1) Dilute a quantity of the injection to produce a solution containing the equivalent of 0.05% w/v of cefuroxime.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Heat 20 mL of a 0.05% w/v solution of *cefuroxime sodium BPCRS* in a water bath at 80° for 15 minutes, cool and inject immediately (generation of descarbamoylcefuroxime).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 274 nm.
(f) Inject 15 µL of each solution.

MOBILE PHASE

17 volumes of *methanol* and 83 volumes of a buffer solution prepared by dissolving 0.7708 g of *ammonium acetate* in 996 mL of *water*, adding 4 mL of *triethylamine* and adjusting the pH to 3.6 with *acetic acid*.

www.webofpharma.com

https://thuocngocanh.com/

When the chromatograms are recorded under the prescribed conditions the retention time of cefuroxime is about 8.4 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to cefuroxime and descarbamoylcefuroxime is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to descarbamoylcefuroxime (located by comparison with the chromatogram obtained with solution (3)) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Bacterial endotoxins

Carry out the test for *bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, in *water BET* to give a solution containing the equivalent of 10 mg of cefuroxime per mL (solution A). The endotoxin limit concentration of solution A is 1.0 IU per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*. Prepare the solutions immediately before use or store at 2° to 8°.

(1) Dilute a quantity of the injection to produce a solution containing the equivalent of 0.05% w/v of cefuroxime.
(2) 0.055% w/v of *cefuroxime sodium BPCRS*.
(3) Heat 20 mL of solution (2) in a water bath at 80° for 15 minutes, cool and inject immediately (generation of descarbamoylcefuroxime).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 274 nm.
(f) Inject 15 µL of each solution.

MOBILE PHASE

17 volumes of *methanol* and 83 volumes of a buffer solution prepared by dissolving 0.7708 g of *ammonium acetate* in 996 mL of *water*, adding 4 mL of *triethylamine* and adjusting the pH to 3.6 with *acetic acid*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to cefuroxime and descarbamoylcefuroxime is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{16}N_4O_8S$ in the injection from the declared content of $C_{16}H_{15}N_4NaO_8S$ in *cefuroxime sodium BPCRS*.

Each mg of $C_{16}H_{15}N_4NaO_8S$ is equivalent to 0.9508 mg of $C_{16}H_{16}N_4O_8S$.

STORAGE

Cefuroxime Intracameral Injection should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of cefuroxime.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

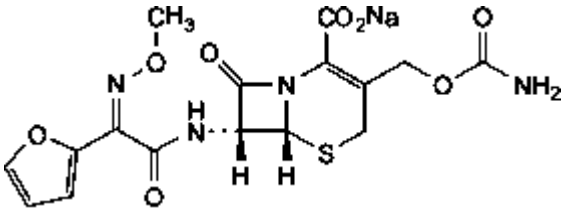
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cefuroxime Sodium

General Notices

(Ph. Eur. monograph 0992)



$C_{16}H_{15}N_4NaO_8S$ 446.4 *56238-63-2*

Action and use

Cephalosporin antibacterial.

Preparations

Cefuroxime Eye Drops

Cefuroxime Injection

Cefuroxime Intracameral Injection

Ph Eur

DEFINITION

Sodium (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, slightly hygroscopic powder.

Solubility

www.webofpharma.com

https://thuvienthuocngocanh.com/

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *cefuroxime sodium CRS*.

B. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1). The absorbance (2.2.25) of solution S measured at 450 nm is not greater than 0.25.

pH (2.2.3)

5.5 to 8.5.

Dilute 2 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Specific optical rotation (2.2.7)

+ 59 to + 66 (anhydrous substance).

Dissolve 0.500 g in *acetate buffer solution pH 4.6 R* and dilute to 25.0 mL with the same buffer solution.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or keep at 2-8 °C.*

Test solution (a) Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with *water R*.

Reference solution (a) Dissolve 25.0 mg of *cefuroxime sodium CRS* in *water R* and dilute to 25.0 mL with the same solvent. Dilute 5.0 mL to 50.0 mL with *water R*.

Reference solution (b) Place 20 mL of reference solution (a) in a water-bath at 80 °C for 15 min. Cool and inject immediately.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with *water R*.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *hexylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 1 volume of *acetonitrile R* and 99 volumes of an acetate buffer solution pH 3.4, prepared by dissolving 6.01 g of *glacial acetic acid R* and 0.68 g of *sodium acetate R* in *water R* and diluting to 1000 mL with the same solvent.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 273 nm.

Injection 20 µL loop injector; inject test solution (a) and reference solutions (b) and (c).

Run time 4 times the retention time of cefuroxime.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to cefuroxime and impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

***N*,*N*-Dimethylaniline** (*2.4.26, Method B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.5 per cent *m/m*.

Water (*2.5.12*)

Maximum 3.5 per cent, determined on 0.400 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.10 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

www.webofpharma.com

https://thuocngocanh.com/

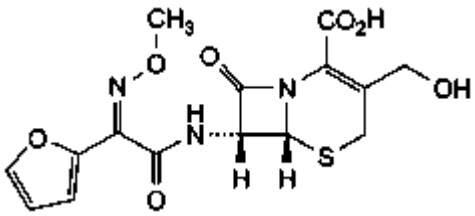
Injection Test solution (b) and reference solution (a).

Calculate the percentage content of cefuroxime sodium.

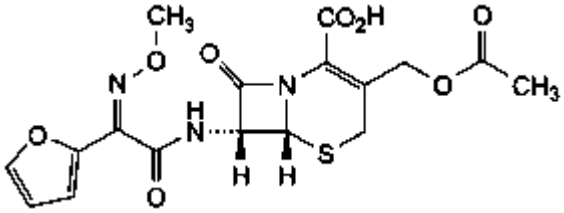
STORAGE

In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

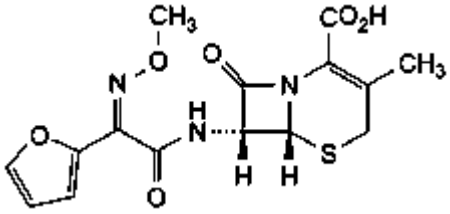
IMPURITIES



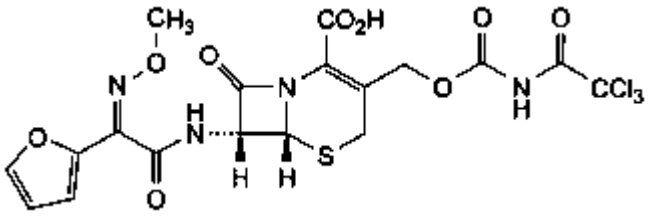
A. (6*R*,7*R*)-7-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (descarbamoylcefuroxime),



B. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



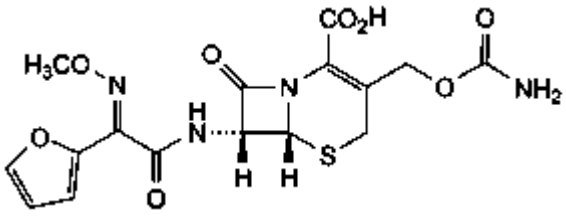
C. (6*R*,7*R*)-7-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



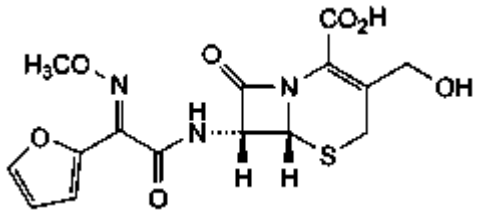
D. (6*R*,7*R*)-7-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-8-oxo-3-[[[(trichloroacetyl)carbamoyl]oxy]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

www.webofpharma.com

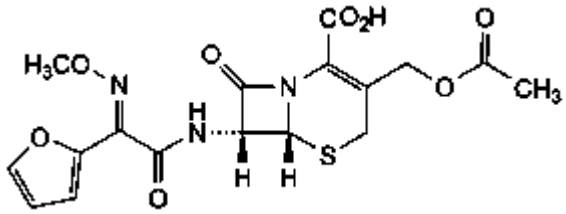
https://thuocngocanh.com/



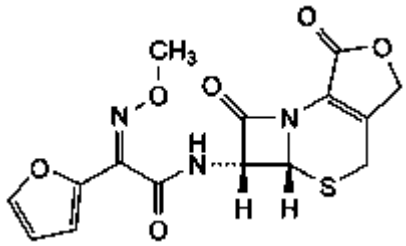
E. (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(*E*)-(furan-2-yl)(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (*trans*-cefuroxime),



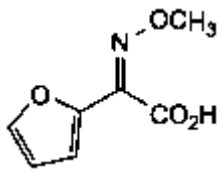
F. (6*R*,7*R*)-7-[[(*E*)-(furan-2-yl)(methoxyimino)acetyl]amino]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



G. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(*E*)-(furan-2-yl)(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



H. (5a*R*,6*R*)-6-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione,



I. (*Z*)-(furan-2-yl)(methoxyimino)acetic acid.

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

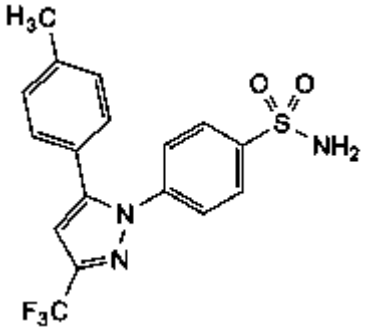
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Celecoxib

General Notices

(Ph. Eur. monograph 2591)



$C_{17}H_{14}F_3N_3O_2S$ 381.4 *169590-42-5*

Action and use

Cyclo-oxygenase (COX-2) inhibitor; analgesic; anti-inflammatory.

Preparation

Celecoxib Capsules

Ph Eur

DEFINITION

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline or amorphous powder.

Solubility

Practically insoluble in water, freely soluble to soluble in anhydrous ethanol, soluble in methylene chloride.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison celecoxib CRS.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in 2-propanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture water R, methanol R2 (25:75 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of celecoxib CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 3 mg of celecoxib impurity A CRS and 3 mg of celecoxib impurity B CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 25.0 mL with reference solution (a).

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped phenylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 60 °C.

Mobile phase Mix 10 volumes of acetonitrile R1, 30 volumes of methanol R2 and 60 volumes of a 2.7 g/L solution of potassium dihydrogen phosphate R previously adjusted to pH 3.0 with phosphoric acid R.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 25 µL of the test solution and reference solutions (b) and (c).

Run time 1.5 times the retention time of celecoxib.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to celecoxib (retention time = about 27 min): impurity A = about 0.9; impurity B = about 1.1.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity A and celecoxib and minimum 1.8 between the peaks due to celecoxib and impurity B in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— for all impurities, use the concentration of celecoxib in reference solution (c).

Limits:

— *impurity A*: maximum 0.4 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 0.400 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{17}H_{14}F_3N_3O_2S$ taking into account the assigned content of *celecoxib CRS*.

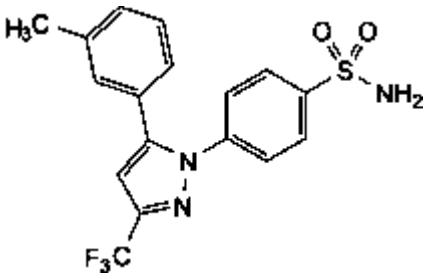
IMPURITIES

Specified impurities *A*.

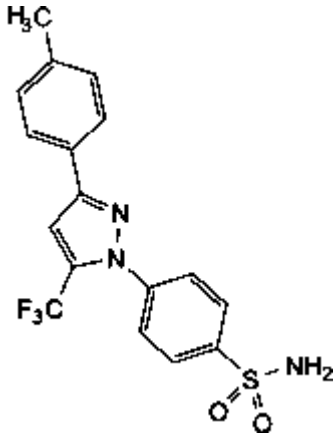
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B*.

www.webofpharma.com

https://thuocngocanh.com/



A. 4-[5-(3-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide,



B. 4-[3-(4-methylphenyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Celecoxib Capsules

General Notices

Action and use

Cyclo-oxygenase (COX-2) inhibitor; analgesic; anti-inflammatory.

DEFINITION

Celecoxib Capsules contain Celecoxib.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of celecoxib, $C_{17}H_{14}F_3N_3O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing 0.1 g of Celecoxib with 25 mL of *ether*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the reference spectrum of celecoxib (*RS497*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 1000 mL of a solution containing 1% w/v of *sodium dodecyl sulfate* in 0.04M *anhydrous trisodium orthophosphate*, adjusted to pH 12 with *orthophosphoric acid* or *strong sodium hydroxide solution*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute the filtrate, if necessary, with dissolution medium to produce a solution expected to contain 0.005% w/v of Celecoxib.

(2) 0.005% w/v of *celecoxib BPCRS* in the dissolution medium.

(3) 0.048% w/v of *celecoxib BPCRS*, 0.00024% w/v of *celecoxib impurity A EPCRS* and 0.00024% w/v of *celecoxib Impurity B EPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped phenylsilyl silica gel for chromatography* (5 µm) (Supelco Supelcosil LC-DP is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

10 volumes of *acetonitrile R1*, 30 volumes of *methanol R1* and 60 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity A and celecoxib is at least 1.5;

the *resolution* between the peaks due to celecoxib and impurity B is at least 1.8.

DETERMINATION OF CONTENT

Calculate the total content of celecoxib, $C_{17}H_{14}F_3N_3O_2S$, in the medium from the chromatograms obtained and using the declared content of $C_{17}H_{14}F_3N_3O_2S$, in *celecoxib BPCRS*.

LIMITS

The amount of celecoxib released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol* (75%).

(1) Shake a quantity of the powdered capsule contents with a sufficient volume to produce a solution containing 0.05% w/v of Celecoxib. Filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.

(3) 0.048% w/v of *celecoxib BPCRS*, 0.00024% w/v of *celecoxib impurity A EPCRS* and 0.00024% w/v of *celecoxib Impurity B EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to celecoxib (retention time about 19 minutes) are: impurity 1, about 0.8; impurity A, about 0.9; impurity B, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

www.webofpharma.com

https://thuocngocanh.com/

the *resolution* between the peaks due to impurity A and celecoxib is at least 1.5;

the *resolution* between the peaks due to celecoxib and impurity B is at least 1.8.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh the contents of 20 capsules and mix. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (75%)*.

(1) Mix a quantity of the capsules containing 200 mg of Celecoxib with 80 mL with the aid of ultrasound for 10 minutes, shake for 30 minutes, dilute to 100 mL and filter. Dilute 1 volume of the resulting solution to 4 volumes.
(2) 0.05% w/v of *celecoxib BPCRS*.
(3) 0.048% w/v of *celecoxib BPCRS*, 0.00024% w/v of *impurity A EPCRS* and 0.00024% w/v of *impurity B EPCRS.*

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity A and celecoxib is at least 1.5;

the *resolution* between the peaks due to celecoxib and impurity B is at least 1.8.

DETERMINATION OF CONTENT

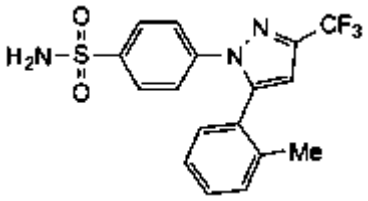
Calculate the content of $C_{17}H_{14}F_3N_3O_2S$, in the capsules from the chromatograms obtained and using the declared content of $C_{17}H_{14}F_3N_3O_2S$, in *celecoxib BPCRS.*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Celecoxib* and:

www.webofpharma.com

https://thuathuocngocanh.com/



1. 4-[5-(2-methylphenyl)-3-trifluoromethyl-1*H*-pyrazol-1-yl]benzenesulfonamide

© Crown Copyright 2022

www.webofpharma.com

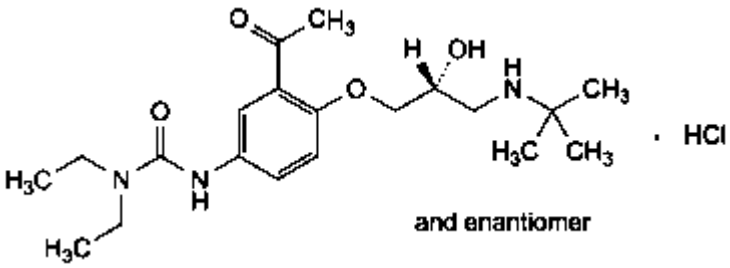
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Celiprolol Hydrochloride

General Notices

(Ph. Eur. monograph 1632)



$C_{20}H_{34}ClN_3O_4$ 416.0 *57470-78-7*

Action and use

Beta-adrenoceptor antagonist.

Preparation

Celiprolol Tablets

Ph Eur

DEFINITION

N-[3-Acetyl-4-[(2*RS*)-3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-*N*′,*N*′-diethylurea hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or very slightly yellow, crystalline powder.

Solubility

Freely soluble in water and in methanol, soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *celiprolol hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Optical rotation (2.2.7)

-0.10° to + 0.10°.

Dissolve 1.0 g in *water R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use, except reference solution (a).*

Test solution Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) In order to prepare impurity A *in situ*, dissolve 10 mg of the substance to be examined in mobile phase A and dilute to 2 mL with mobile phase A and allow to stand for 24 h.

Reference solution (b) Dissolve 10 mg of *celiprolol for system suitability CRS* (containing impurities B and F) in mobile phase A and dilute to 2 mL with mobile phase A.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 0.2 mL of *trifluoroacetic acid R*, 0.6 mL of *pentafluoropropanoic acid R*, 63 mL of *acetonitrile for chromatography R* and 91 mL of *tetrahydrofuran R*; dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	100 → 80	0 → 20

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 232 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *celiprolol for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and F; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to celiprolol (retention time = about 10 min): impurity A = about 0.3; impurity B = about 1.4; impurity F = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurities B and F.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 4.0;

— for each impurity, use the concentration of celiprolol hydrochloride in reference solution (c).

Limits:

— *impurity A*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.350 g under an atmosphere of nitrogen in 50 mL of *ethanol (96 per cent) R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 41.60 mg of $C_{20}H_{34}ClN_3O_4$.

www.webofpharma.com

https://thuocngocanh.com/

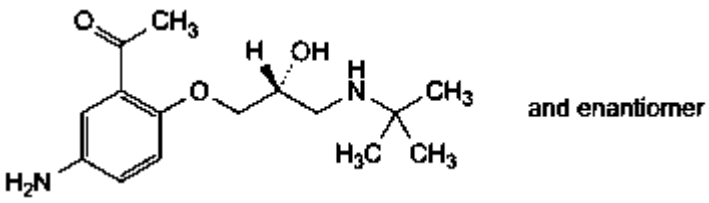
STORAGE

Protected from light.

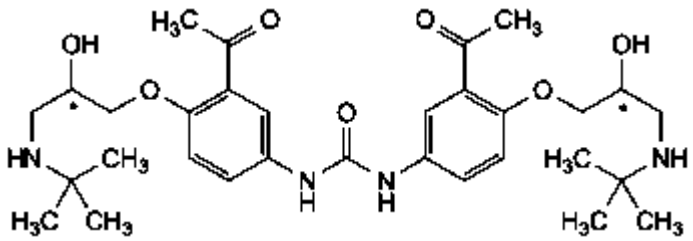
IMPURITIES

Specified impurities A.

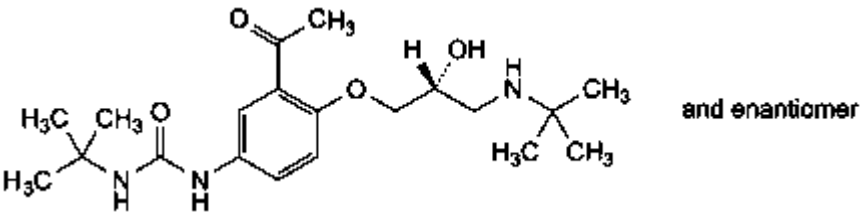
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, F, G, H, I.



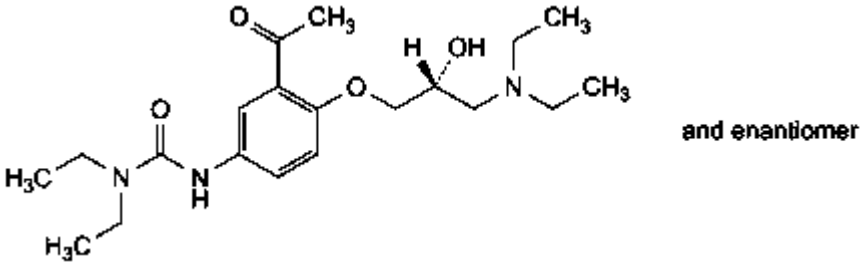
A. 1-[5-amino-2-[(2*RS*)-3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]ethan-1-one,



B. *N*,*N*′-bis[3-acetyl-4-[(2Ξ)-3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]urea,



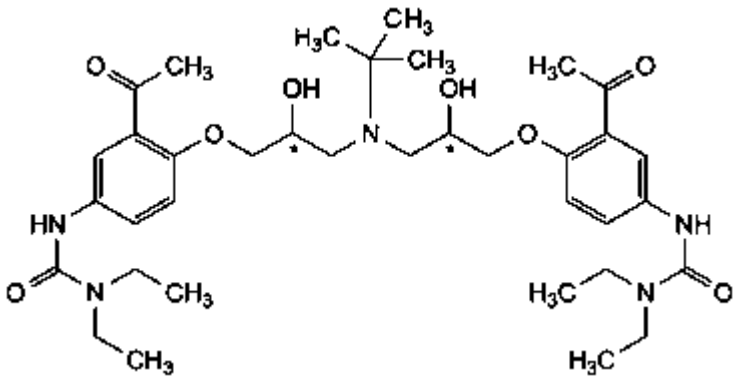
C. *N*-[3-acetyl-4-[(2*RS*)-3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-*N*′-*tert*-butylurea,



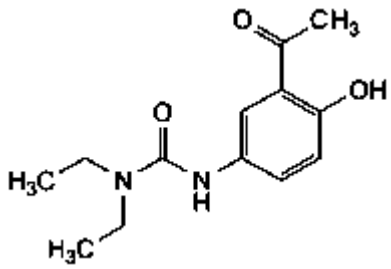
D. *N*-[3-acetyl-4-[(2*RS*)-3-(diethylamino)-2-hydroxypropoxy]phenyl]-*N*′,*N*′-diethylurea,

www.webofpharma.com

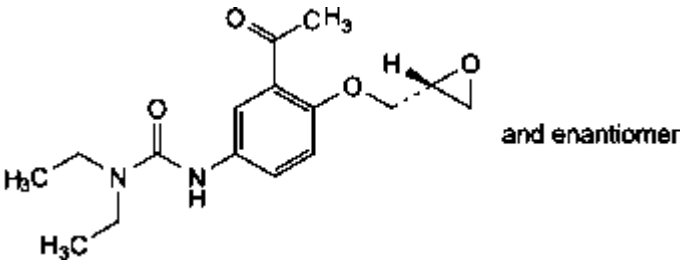
https://thuocngocanh.com/



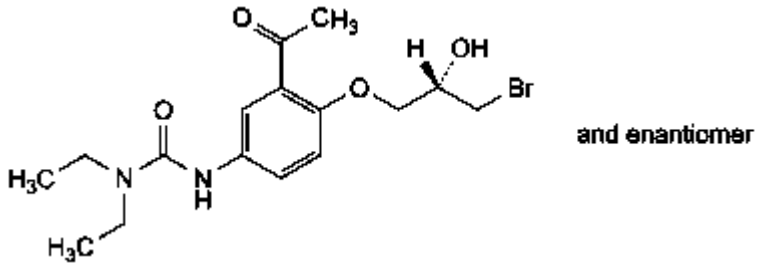
E. *N*-[3-acetyl-4-[(2Ξ)-3-[[(2Ξ)-3-[2-acetyl-4-[(diethylcarbamoyl)amino]phenoxy]-2-hydroxypropyl](*tert*-butyl)amino]-2-hydroxypropoxy]phenyl]-*N*′,*N*′-diethylurea,



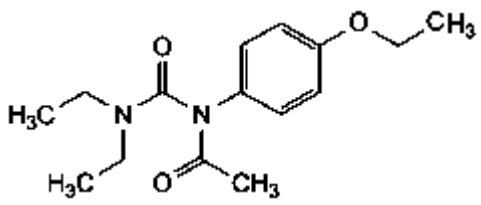
F. *N*-(3-acetyl-4-hydroxyphenyl)-*N*′,*N*′-diethylurea,



G. *N*-(3-acetyl-4-[[(*RS*)-oxiranyl]methoxy]phenyl)-*N*′,*N*′-diethylurea,



H. *N*-[3-acetyl-4-[(2*RS*)-3-bromo-2-hydroxypropoxy]phenyl]-*N*′,*N*′-diethylurea,



www.webofpharma.com

https://thuocngocanh.com/

I. *N*-acetyl-*N*-(4-ethoxyphenyl)-*N*′,*N*′-diethylurea.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Celiprolol Tablets

General Notices

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Celiprolol Tablets contain Celiprolol Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of celiprolol hydrochloride, $C_{20}H_{33}N_3O_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix with the aid of ultrasound a quantity of the powdered tablets containing 200 mg of Celiprolol Hydrochloride with 100 mL of *dichloromethane* for 30 minutes, filter (Whatman filter paper No. 42 is suitable), remove the dichloromethane using a rotary evaporator and dry the residue over *phosphorus pentoxide* at 110° at a pressure not exceeding 2 kPa for 1 hour. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of celiprolol hydrochloride (*RS 420*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water* at a temperature of 37° as the medium.

PROCEDURE

(1) Withdraw a sample of 10 mL of the medium and filter; to 1 volume of the filtrate add sufficient *water* to produce 20 volumes and filter using a 0.45 µm membrane filter. Measure the *absorbance* of the filtrate, suitably diluted with *water* if necessary, at the maximum at 231 nm, Appendix II B, using *water* in the reference cell.

(2) Measure the *absorbance* of a 0.011% w/v solution of *celiprolol hydrochloride BPCRS* in the dissolution medium at the maximum at 231 nm, Appendix II B, using *water* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of celiprolol hydrochloride, $C_{20}H_{33}N_3O_4$,HCl, in the medium using the declared content of $C_{20}H_{33}N_3O_4$,HCl in *celiprolol hydrochloride BPCRS*.

Related substances

Carry out method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Celiprolol Hydrochloride in 100 mL of the mobile phase for 15 minutes with occasional shaking, cool and filter using a 0.45-µm membrane filter.
(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase and further dilute 1 volume of this solution to 20 volumes with the mobile phase.
(3) Prepare a solution containing 0.1% w/v of *celiprolol hydrochloride BPCRS* in *water*, add 5 drops of 5M *sodium hydroxide* and heat at 70° for 20 minutes (generation of impurity A).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Waters µBondapak is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use ambient column temperature.
(e) Use a detection wavelength of 233 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

A mixture of 25 volumes of *acetonitrile* and 75 volumes of 0.025M *sodium dihydrogen phosphate monohydrate* adjusted to pH 3.0 with 3M *orthophosphoric acid*. If necessary adjust the composition of the mobile phase so that, in the chromatogram obtained with solution (3), the peak due to celiprolol impurity A is resolved from the solvent front.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the peak due to celiprolol impurity A is resolved from the solvent front.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to celiprolol impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

not more than one such peak has an area not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area of less than a fifth of the area of the peak in the chromatogram obtained with solution (2) (0.02%).

ASSAY

Carry out method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Celiprolol Hydrochloride in 100 mL of the mobile phase for 15 minutes, cool and filter. Dilute 1 volume of the filtrate to 50 volumes with the mobile phase and filter using a 0.45 µm membrane filter.

(2) 0.002% w/v solution of *celiprolol hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

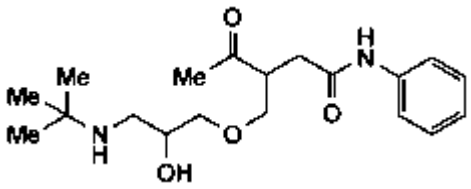
Calculate the content of $C_{20}H_{33}N_3O_4$,HCl in the tablets using the declared content of $C_{20}H_{33}N_3O_4$,HCl in *celiprolol hydrochloride BPCRS*.

STORAGE

Celiprolol Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Celiprolol Hydrochloride and the following:



1. 3-acetyl-4-{3-(1,1-dimethyl-ethylamino)-2-hydroxy}propoxybutyranilide

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Cellacefate[1]

General Notices

(Cellulose Acetate Phthalate, Ph. Eur. monograph 0314)

9004-38-0

Action and use

Enteric coating in pharmaceutical products.

Ph Eur

DEFINITION

Partly *O*-acetylated and *O*-phthalylated cellulose.

Content

— *phthaloyl groups* ($C_8H_5O_3$; M_r 149.1): 30.0 per cent to 36.0 per cent (anhydrous and acid-free substance);

— *acetyl groups* (C_2H_3O; M_r 43.04): 21.5 per cent to 26.0 per cent (anhydrous and acid-free substance).

♦ CHARACTERS

Appearance

White or almost white, free-flowing powder or colourless flakes, hygroscopic.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in diethylene glycol, practically insoluble in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.♦

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *cellulose acetate phthalate CRS*.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Viscosity (*2.2.9*)

45 mPa·s to 90 mPa·s, determined at 25 ± 0.2 °C.

Dissolve 15 g, calculated with reference to the anhydrous substance, in 85 g of a mixture of 1 part by mass of *water R* and 249 parts by mass of *acetone R*.

Free acid

Maximum 3.0 per cent, calculated as phthalic acid (anhydrous substance).

Shake 3.0 g for 2 h with 100 mL of a 50 per cent *V/V* solution of *methanol R* and filter. Wash the flask and the filter with 2 quantities, each of 10 mL, of a 50 per cent *V/V* solution of *methanol R*. Combine the filtrate and washings, add 0.1 mL of *phenolphthalein solution R1* and titrate with *0.1 M sodium hydroxide* until a faint pink colour is obtained. Carry out a blank titration using 120 mL of a 50 per cent *V/V* solution of *methanol R*.

1 mL of *0.1 M sodium hydroxide* is equivalent to 8.3 mg of free acid, calculated as phthalic acid.

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.500 g.

Carry out the test using a mixture of 2 volumes of *methylene chloride R* and 3 volumes of *anhydrous ethanol R*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Phthaloyl groups

Dissolve 1.000 g in 50 mL of a mixture of 2 volumes of *acetone R* and 3 volumes of *ethanol (96 per cent) R*. Add about 0.1 mL of *phenolphthalein solution R1* and titrate with *0.1 M sodium hydroxide*. Carry out a blank titration.

Calculate the percentage content of phthaloyl groups (*P*) using the following expression:

$$\frac{14910\left(n_1 - n_2\right)}{(100 - a)(100 - S)m} - \frac{179.5S}{(100 - S)}$$

a	=	percentage content of water (see Tests);
m	=	mass of the substance to be examined, in grams;
n_1	=	volume of *0.1 M sodium hydroxide* used in the titration, in millilitres;
n_2	=	volume of *0.1 M sodium hydroxide* used in the blank titration, in millilitres;
S	=	percentage content of free acid (see Tests).

www.webofpharma.com

https://thuocngocanh.com/

Acetyl groups

To 0.100 g add 25.0 mL of *0.1 M sodium hydroxide* and heat on a water-bath under a reflux condenser for 30 min. Cool, add about 0.1 mL of *phenolphthalein solution R1* and titrate with *0.1 M hydrochloric acid*. Carry out a blank titration.

Calculate the percentage content of acetyl groups using the following expression:

$$\left[\frac{4305\left(n_2 - n_1\right)}{(100 - a)(100 - S)m} - \frac{51.82S}{(100 - S)}\right] - 0.5772P$$

a	=	percentage content of water (see Tests);
m	=	mass of the substance to be examined, in grams;
n_1	=	volume of *0.1 M hydrochloric acid* used in the titration, in millilitres;
n_2	=	volume of *0.1 M hydrochloric acid* used in the blank titration, in millilitres;
P	=	percentage content of phthaloyl groups;
S	=	percentage content of free acid (see Tests).

♦ STORAGE

In an airtight container.♦

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for cellulose acetate phthalate used as film former in gastro-resistant tablets and capsules.

Viscosity

See Tests.

Solubility of a film

Dissolve about 0.15 g in 1 mL of *acetone R* and pour onto a clear glass plate. A film is formed. Take a piece of the film and place it in a flask containing *0.1 M hydrochloric acid*. It does not dissolve. Then place the piece of film in a flask containing *phosphate buffer solution*

www.webofpharma.com

https://thuocngocanh.com/

pH 6.8 R. It dissolves.

Phthaloyl groups

See Assay.

Acetyl groups

See Assay.◊

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cellulose Acetate[1]

General Notices

(Ph. Eur. monograph 0887)

Action and use

Excipient.

Ph Eur

DEFINITION

Partly or completely *O*-acetylated cellulose.

Content

— *acetyl groups* (C_2H_3O; M_r 43.04): 29.0 per cent to 44.8 per cent (dried substance); 90.0 per cent to 110.0 per cent of the nominal content (dried substance).

CHARACTERS

Appearance

White, yellowish-white or greyish-white, hygroscopic powder or granules.

Solubility

Practically insoluble in water, soluble in acetone, in formic acid and in a mixture of equal volumes of methanol and methylene chloride, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cellulose acetate CRS*.

Preparation Prepare a 20 g/L solution of cellulose acetate, previously dried, in *acetone R* (mono- or diester) or in *methylene chloride R* (di- or triester), and spread 1 drop of the solution between 2 sodium chloride plates; separate the plates, heat them both at 105 °C for 1 h, and reassemble the dried plates.

TESTS

Free acid

www.webofpharma.com

https://thuocngocanh.com/

Free acid

Maximum 0.1 per cent, calculated as acetic acid (dried substance).

To 5.00 g in a 250 mL conical flask, add 150 mL of *carbon dioxide-free water R*, insert the stopper, swirl the suspension gently and allow to stand for 3 h. Filter, then wash the flask and the filter with *carbon dioxide-free water R*, adding the washings to the filtrate. Add 0.1 mL of *phenolphthalein solution R1* and titrate the combined filtrate and washings with *0.01 M sodium hydroxide* until a pale pink colour is obtained.

1 mL of *0.01 M sodium hydroxide* is equivalent to 0.6005 mg of free acid, calculated as acetic acid.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

ASSAY

A. Cellulose acetate containing not more than 42.0 per cent of acetyl groups.

To 2.000 g in a 500 mL conical flask, add 100 mL of *acetone R* and 5-10 mL of *water R*. Close the flask and stir with a magnetic stirrer until dissolution is complete. Add 30.0 mL of *1 M sodium hydroxide* with constant stirring. A finely divided precipitate of regenerated cellulose, free from lumps, is obtained. Close the flask and stir with a magnetic stirrer for 30 min. Add 100 mL of *water R* at 80 °C, washing down the sides of the flask, stir for 2 min and cool to room temperature. Titrate with *0.5 M sulfuric acid*, using 0.1 mL of *phenolphthalein solution R1* as indicator. Carry out a blank titration.

Calculate the percentage content of acetyl groups using the following expression:

$$\frac{4.305\left(n_2 - n_1\right)}{(100 - d) \times m} \times 100$$

d	=	loss on drying as a percentage;
m	=	mass of the substance to be examined, in grams;
n_1	=	volume of *0.5 M sulfuric acid* used in the titration, in millilitres;
n_2	=	volume of *0.5 M sulfuric acid* used in the blank titration, in millilitres.

www.webofpharma.com

https://thuocngocanh.com/

B. Cellulose acetate containing more than 42.0 per cent of acetyl groups.

To 2.000 g in a 500 mL conical flask, add 30 mL of *dimethyl sulfoxide R* and 100 mL of *acetone R*. Close the flask and stir with a magnetic stirrer for 16 h. Add 30.0 mL of *1 M sodium hydroxide* with constant stirring. Close the flask and stir with a magnetic stirrer for 6 min. Allow to stand without stirring for 60 min. Resume stirring and add 100 mL of *water R* at 80 °C, washing down the sides of the flask, stir for 2 min and cool to room temperature. Titrate with *0.5 M hydrochloric acid*, using 0.1 mL of *phenolphthalein solution R1* as indicator. Add 0.5 mL of *0.5 M hydrochloric acid* in excess, stir for 5 min and allow to stand for 30 min. Titrate with *0.5 M sodium hydroxide* until a persistent pink colour is obtained, stirring with a magnetic stirrer. Calculate the net amount of *0.5 M sodium hydroxide* consumed, in millimoles, taking the mean of 2 blank titrations into consideration.

Calculate the percentage content of acetyl groups using the following expression:

$$\frac{4.305 \times n}{(100 - d) \times m} \times 100$$

d	=	loss on drying as a percentage;
m	=	mass of the substance to be examined, in grams;
n	=	net amount of *0.5 M sodium hydroxide* consumed, in millimoles.

STORAGE

In an airtight container.

LABELLING

The label states the nominal percentage content of acetyl groups.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for cellulose acetate used as film former.

Viscosity

Dissolve 10 g in a mixture of 50 mL of *methanol R* and 50 mL of *methylene chloride R* by shaking. Determine the viscosity of this solution at 20 ± 0.1 °C using a rotating viscometer (*2.2.10*).

Acetyl groups

www.webofpharma.com

https://thuvienthuocngocanh.com/

See Assay.

The following characteristics may be relevant for cellulose acetate used as matrix former in prolonged-release tablets.

Viscosity

See test above.

Acetyl groups

See Assay.

Molecular mass distribution (*2.2.30*)

Particle-size distribution (*2.9.31*)

Powder flow (*2.9.36*)

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cellulose Acetate Butyrate

General Notices

(Ph. Eur. monograph 1406)

Action and use

Excipient.

Ph Eur

DEFINITION

Partly or completely *O*-acetylated and *O*-butyrated cellulose.

Content

— *acetyl groups* (C_2H_3O): 2.0 per cent to 30.0 per cent (dried substance); 90.0 per cent to 110.0 per cent of that stated on the label (dried substance);

— *butyryl groups* (C_4H_7O): 16.0 per cent to 53.0 per cent (dried substance); 90.0 per cent to 110.0 per cent of that stated on the label (dried substance).

CHARACTERS

Appearance

White, yellowish-white or greyish-white powder or granules, slightly hygroscopic.

Solubility

Practically insoluble in water, soluble in acetone, in formic acid and in a mixture of equal volumes of methanol and methylene chloride, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *cellulose acetate butyrate CRS*.

The intensity of the bands may vary according to the degree of substitution.

B. It complies with the limits of the assay.

www.webofpharma.com

https://thuvienthuocngocanh.com/

TESTS

Acidity

To 5.00 g in a 250 mL conical flask, add 150 mL of *carbon dioxide-free water R*, insert the stopper, swirl the suspension gently and allow to stand for 3 h. Filter, wash the flask and the filter with *carbon dioxide-free water R*. Combine the filtrate and washings. Add 0.1 mL of *phenolphthalein solution R1*. Not more than 3.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Total ash (*2.4.16*)

Maximum 0.1 per cent.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution To 1.000 g of the substance to be examined in a 500 mL conical flask, add 100 mL of *acetone R* and 10 mL of *water R*. Close the flask and stir with a magnetic stirrer until dissolution is complete. Add 30.0 mL of *1 M sodium hydroxide* with constant stirring. Close the flask and stir with a magnetic stirrer for 30 min. Add 100 mL of hot *water R* at 80 °C, washing down the sides of the flask and stir for 2 min. Cool, centrifuge or filter the suspension and wash the residue with *water R*. Combine the filtrate and washings, adjust to pH 3 with *dilute phosphoric acid R* and dilute to 500.0 mL with *water R*.

Reference solution Dissolve 0.200 g of *glacial acetic acid R* and 0.400 g of *butyric acid R* in *water R*, adjust to pH 3 with *dilute phosphoric acid R* and dilute to 500.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *methanol R*;

— *mobile phase B*: *phosphate buffer solution pH 3.0 R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	5	95
30 - 35	5 → 20	95 → 80
35 - 60	20	80

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
60 - 61	5	95

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Calculate the percentage content of acetic acid and butyric acid using the chromatograms obtained with the 2 solutions. To calculate the percentage content of acetyl (C_2H_3O) and of butyryl (C_4H_7O) groups, multiply the percentage content of acetic acid and butyric acid by 0.717 and 0.807, respectively.

STORAGE

In an airtight container.

LABELLING

The label states the nominal percentage content of acetyl and butyryl groups.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetirizine Capsules

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Cetirizine Capsules contain Cetirizine Hydrochloride in a suitable aqueous vehicle.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of cetirizine hydrochloride, $C_{21}H_{25}ClN_2O_3,2HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the capsule contents, if necessary, to contain 0.1% w/v of Cetirizine Hydrochloride, filter (a 0.45-µm nylon filter is suitable) and use the filtrate.

(2) 0.1% w/v of *cetirizine hydrochloride BPCRS*.

(3) 0.1% w/v of *cetirizine hydrochloride BPCRS* and 0.1% w/v of *chlorphenamine maleate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://nhathuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter, and dilute the filtrate with sufficient of the dissolution medium to give a solution expected to contain about 0.0005% w/v of Cetirizine Hydrochloride.

(2) 0.0005% w/v solution of *cetirizine hydrochloride BPCRS* in *water*.

(3) 0.02% w/v of *cetirizine impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18(2) is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile* and 70 volumes of 0.0025M *potassium dihydrogen orthophosphate*, previously adjusted to pH 1.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cetirizine and cetirizine impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{25}ClN_2O_3,2HCl$ in the medium using the declared content of $C_{21}H_{25}ClN_2O_3,2HCl$ in *cetirizine hydrochloride BPCRS*.

LIMITS

The amount of cetirizine hydrochloride released is not less than 80% (Q) of the stated amount.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Dilute a quantity of the capsule contents, if necessary, to produce a solution containing 0.02% w/v of Cetirizine Hydrochloride and filter through a 0.45-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume to 10 volumes.

(3) 0.02% w/v of *cetirizine impurity standard BPCRS*.

(4) 0.00006% w/v of *cetirizine N-oxide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18(2) is suitable).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 17 volumes of *acetonitrile* and 83 volumes of *water* previously adjusted to pH to 1.5 with *orthophosphoric acid*.

Mobile phase B 35 volumes of *acetonitrile* and 65 volumes of *water* previously adjusted to pH 1.5 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-50	100→0	0→100	linear gradient
50-53	0	100	isocratic
53-54	0→100	100→0	linear gradient
54-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to cetirizine (retention time about 41 minutes) are: impurity A, about 0.7; impurity G, about 0.88 and impurity B, about 0.96.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cetirizine and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity A using solution (3) and the chromatogram supplied with *cetirizine impurity standard BPCRS* and multiply the area of this peak by a correction factor of 0.7.

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak due to cetirizine *N*-oxide is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

The total impurity content is not greater than 1.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%)

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the mixed contents of 20 capsules to produce a solution containing 0.002% w/v of Cetirizine Hydrochloride and filter (a 0.45-µm nylon filter is suitable).
(2) 0.002% w/v of *cetirizine hydrochloride BPCRS*.
(3) 0.02% w/v of *cetirizine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

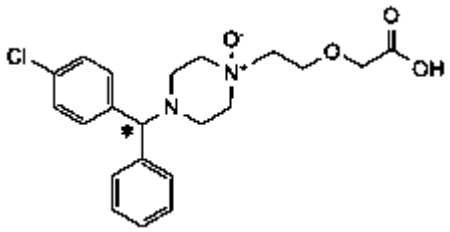
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cetirizine and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{25}ClN_2O_3,2HCl$ in the capsules using the declared content of $C_{21}H_{25}ClN_2O_3,2HCl$ in *cetirizine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and G listed under Cetirizine Hydrochloride and the following.



rac-1-[2-(carboxymethoxy)ethyl]-4-[(4-chlorophenyl)(phenyl)methyl]piperazine N^1-oxide (Cetirizine *N*-oxide).

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products
Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

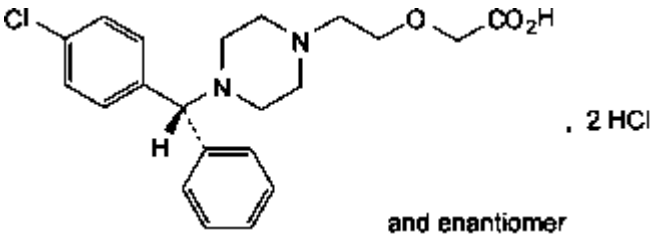
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetirizine Hydrochloride

General Notices

(Cetirizine Dihydrochloride, Ph. Eur. monograph 1084)



$C_{21}H_{27}Cl_3N_2O_3$ 461.8 *83881-52-1*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Preparations

Cetirizine Capsules

Cetirizine Oral Solution

Cetirizine Tablets

Ph Eur

DEFINITION

(*RS*)-2-[2-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, practically insoluble in acetone and in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20.0 mg in 50 mL of a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 10.0 mL of this solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Spectral range 210-350 nm.

Absorption maximum At 231 nm.

Specific absorbance at the absorption maximum 359 to 381.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *cetirizine dihydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *cetirizine dihydrochloride CRS* in *water R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *chlorphenamine maleate CRS* in *water R* and dilute to 5 mL with the same solvent. Mix 1 mL of the solution and 1 mL of reference solution (a).

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *ammonia R*, *methanol R*, *methylene chloride R* (1:10:90 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In a current of cold air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

pH (2.2.3)

1.2 to 1.8 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *cetirizine dihydrochloride CRS* and 2 mg of *cetirizine impurity A CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *cetirizine for peak identification CRS* (containing impurities B, C, D, E and F) in 5.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm).

Mobile phase *dilute sulfuric acid R*, *water R*, *acetonitrile R* (0.4:6.6:93 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 3 times the retention time of cetirizine.

Identification of impurities Use the chromatogram supplied with *cetirizine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, C, D, E and F; use the chromatogram obtained with reference solution (a) to

www.webofpharma.com

https://thuocngocanh.com/

identify the peak due to impurity A.

Relative retention With reference to cetirizine (retention time = about 9 min): impurity D = about 0.6; impurity B = about 0.8; impurity C = about 0.9; impurity E = about 1.2; impurity F = about 1.37; impurity A = about 1.42.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to cetirizine.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity C = 1.9; impurity D = 0.6; impurity E = 1.3; impurity F = 1.9;

— *impurities A, B, C, D, E, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in 70 mL of a mixture of 30 volumes of *water R* and 70 volumes of *acetone R*. Titrate with *0.1 M sodium hydroxide* to the 2nd point of inflexion. Determine the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 15.39 mg of $C_{21}H_{27}Cl_3N_2O_3$.

STORAGE

Protected from light.

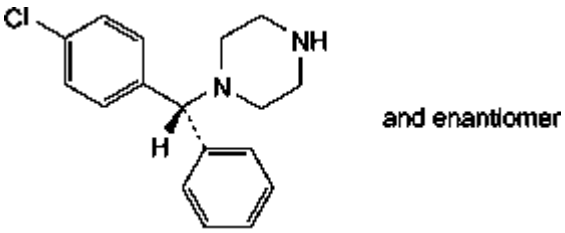
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

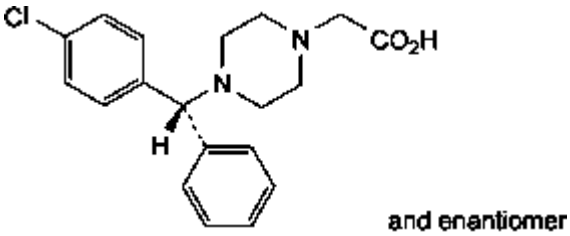
www.webofpharma.com

https://thuocngocanh.com/

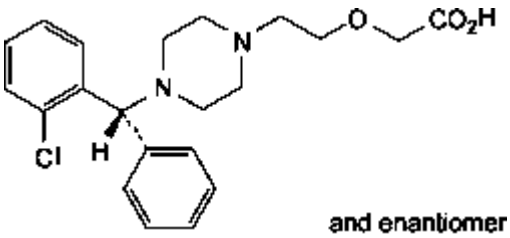
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) G.



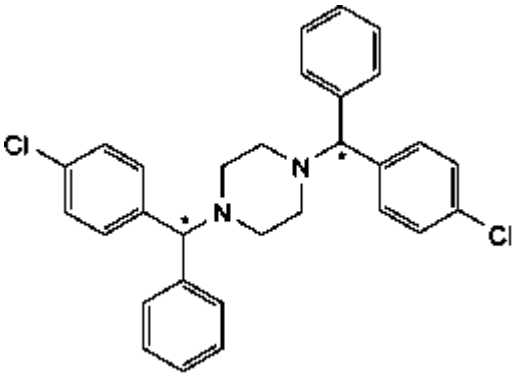
A. (*RS*)-1-[(4-chlorophenyl)phenylmethyl]piperazine,



B. (*RS*)-2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]acetic acid,



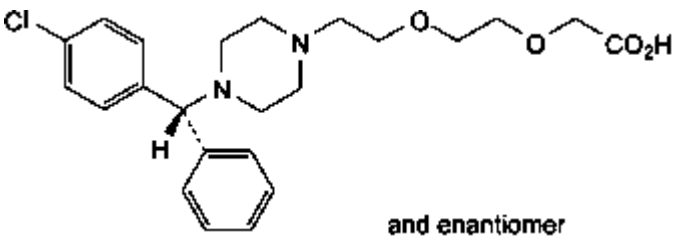
C. (*RS*)-2-[2-[4-[(2-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid,



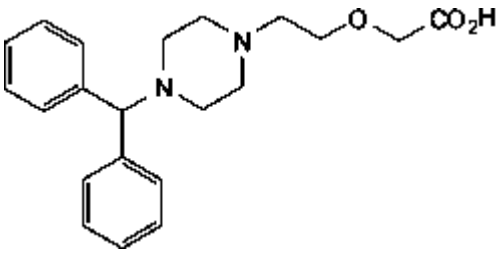
D. 1,4-bis[(4-chlorophenyl)phenylmethyl]piperazine,

www.webofpharma.com

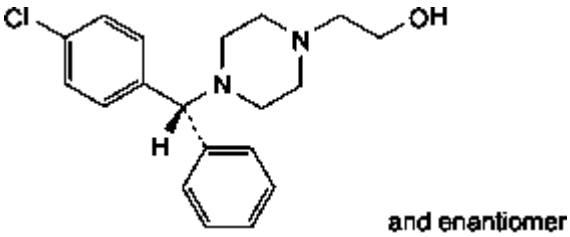
https://thuocngocanh.com/



E. (*RS*)-2-[2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]ethoxy]acetic acid (ethoxycetirizine),



F. 2-[2-[4-(diphenylmethyl)piperazin-1-yl]ethoxy]acetic acid,



G. (*RS*)-2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethan-1-ol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetirizine Oral Solution

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Cetirizine Oral Solution is a solution of Cetirizine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of cetirizine hydrochloride, $C_{21}H_{25}ClN_2O_3,2HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the oral solution, if necessary, to contain 0.1% w/v of Cetirizine Hydrochloride, filter through a 0.45-µm nylon filter and use the filtrate.

(2) 0.1% w/v of *cetirizine hydrochloride BPCRS*.

(3) 0.1% w/v of *cetirizine hydrochloride BPCRS* and 0.1% w/v of *chlorphenamine maleate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia*, 10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

Disregard any spots due to excipients.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Dilute a weighed quantity of the oral solution, if necessary, to contain 0.02% w/v of Cetirizine Hydrochloride and filter through a 0.45-µm nylon filter.
(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 2 volumes of the resulting solution to 10 volumes.
(3) Dilute 1 volume of solution (2) to 4 volumes.
(4) 0.02% w/v of *cetirizine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18(2) is suitable).
(b) Use gradient elution and the mobile phases described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 17 volumes of *acetonitrile* and 83 volumes of *water* previously adjusted to pH to 1.5 with *orthophosphoric acid*.

Mobile phase B 35 volumes of *acetonitrile* and 65 volumes of *water* previously adjusted to pH 1.5 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A % v/v	Mobile phase B % v/v	Comment
0-50	100→0	0→100	linear gradient
50-53	0	100	isocratic
53-54	0→100	100→0	linear gradient
54-60	100	0	re-equilibration

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to cetirizine and cetirizine impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity A using solution (4) and the chromatogram supplied with *cetirizine impurity standard BPCRS* and multiply the area of this peak by a correction factor of 0.7.

the areas of any peaks corresponding to impurities A, B or G are not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the total content of impurities is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a weighed quantity of the oral solution to contain 0.002% w/v of Cetirizine Hydrochloride and filter through a 0.45-µm nylon filter.
(2) 0.002% w/v of *cetirizine hydrochloride BPCRS*.
(3) 0.02% w/v of *cetirizine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18(2) is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile* and 70 volumes of 0.0025M *potassium dihydrogen orthophosphat*e, previously adjusted to pH 1.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cetirizine and cetirizine impurity B is at least 1.5.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuathuocngocanh.com/

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{21}H_{25}ClN_2O_3$,2HCl, weight in volume, using the declared content of $C_{21}H_{25}ClN_2O_3$,2HCl in *cetirizine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and G listed under Cetirizine Hydrochloride.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetirizine Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Cetirizine Tablets contain Cetirizine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of cetirizine hydrochloride, $C_{21}H_{25}ClN_2O_3,2HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Cetirizine Hydrochloride with 20 mL of *absolute ethanol*, filter (Whatman GF/C is suitable), evaporate the filtrate and dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of cetirizine hydrochloride *(RS 456)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of 10 mL of the medium, filter and dilute the filtrate with sufficient of the dissolution medium to give a solution expected to contain about 0.00050% w/v of Cetirizine Hydrochloride. Measure the *absorbance* of this solution, Appendix II B, at the maximum wavelengths at 230 nm and at 260 nm using the dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *cetirizine hydrochloride BPCRS* in *water* at the maximum wavelengths at 230 nm and 260 nm using the dissolution medium in the reference cell and calculate the difference between the two readings (ΔA) for each measurement.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of Cetirizine Hydrochloride, $C_{21}H_{25}ClN_2O_3,2HCl$, in the medium using the values of ΔA and from the declared content of $C_{21}H_{25}ClN_2O_3,2HCl$ in *cetirizine hydrochloride BPCRS*.

LIMITS

The amount of cetirizine hydrochloride released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Shake a quantity of the powdered tablets containing 20 mg of Cetirizine Hydrochloride with 20 mL of the mobile phase A, filter through a 0.45-µm nylon filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 5 volumes.
(3) Dilute 1 volume of solution (2) to 2 volumes.
(4) 0.02% w/v of *cetirizine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18(2) is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 17 volumes of *acetonitrile* and 83 volumes of *water* previously adjusted to pH 1.5 with *orthophosphoric acid*.

Mobile phase B 35 volumes of *acetonitrile* and 65 volumes of *water* previously adjusted to pH 1.5 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A % v/v	Mobile phase B % v/v	Comment
0-50	100→0	0→100	linear gradient
50-53	0	100	isocratic
53-54	0→100	100→0	linear gradient
54-60	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to cetirizine and impurity B is at least 1.5.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

identify any peaks corresponding to impurity A, impurity B and impurity G using solution (4) and the chromatogram supplied with *cetirizine impurity standard BPCRS*.Multiply the area of any peak corresponding to impurity A by a correction factor of 0.7.

the areas of any peaks corresponding to impurities A, B or G are not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of all impurities is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%)

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the powdered tablets containing 20 mg of Cetirizine Hydrochloride in 100 mL and filter through a 0.45-µm nylon filter. Dilute 10 mL of the filtrate to 100 mL with the mobile phase.
(2) 0.002% w/v of *cetirizine hydrochloride BPCRS*.
(3) 0.02% w/v of *cetirizine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18(2) is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile* and 70 volumes of 0.0025M *potassium dihydrogen orthophosphate*, previously adjusted to pH 1.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cetirizine and cetirizine impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{25}ClN_2O_3,2HCl$ in the tablets using the declared content of $C_{21}H_{25}ClN_2O_3,2HCl$ in *cetirizine hydrochloride BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and G listed under Cetirizine Hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetomacrogol Emulsifying Ointment

General Notices

Action and use

Emulsifying agent.

DEFINITION

White Soft Paraffin	500 g
Cetomacrogol Emulsifying Wax	300 g
Liquid Paraffin	200 g

Extemporaneous preparation

The following directions apply.

Melt together and stir until cold.

The ointment complies with the requirements stated under Topical Semi-solid Preparations.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetomacrogol Emulsifying Wax

General Notices

Non-ionic Emulsifying Wax

Action and use

Emulsifying agent.

DEFINITION

Cetostearyl Alcohol	800 g
Macrogol Cetostearyl Ether (22)	200 g

Extemporaneous preparation

The following directions apply.

Melt together and stir until cold.

CHARACTERISTICS

A white or almost white, waxy solid or flakes melting when heated to a clear almost colourless liquid.

Practically insoluble in *water*, producing an emulsion; moderately soluble in *ethanol (96%)*; partly soluble in *ether*.

IDENTIFICATION

A. Incinerate at a temperature not exceeding 450° until free from carbon and cool. The residue is negligible (distinction from Emulsifying Wax).

B. Complies with the test for Sulfated ash.

TESTS

Acid value

Not more than 0.5, Appendix X B.

Refractive index

At 60°, 1.435 to 1.439, Appendix V E.

Solidifying point

www.webofpharma.com

https://thuocngocanh.com/

45° to 53°, Appendix V B, using the following modifications. Place in the inner test tube sufficient of the melted substance to fill the tube to a depth of about 50 mm. Stir the substance gently and steadily, without scraping the wall of the tube, while the tube and its contents are allowed to cool. The temperature at which the level of the mercury in the thermometer remains stationary for a short time is regarded as the solidifying point.

Alkalinity

Dissolve 10 g in 10 mL of *water* and 10 mL of *ethanol (96%)*. Not more than 0.5 mL of *0.1M hydrochloric acid VS* is required for neutralisation using *phenolphthalein solution R1* as indicator.

Hydroxyl value

175 to 192, Appendix X D. Use 3.5 g.

Saponification value

Not more than 2.0, Appendix X G. Use 20 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

© Crown Copyright 2022

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetostearyl Alcohol

General Notices

(Ph. Eur. monograph 0702)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of solid aliphatic alcohols, mainly octadecan-1-ol (stearyl alcohol; $C_{18}H_{38}O$; M_r 270.5) and hexadecan-1-ol (cetyl alcohol; $C_{16}H_{34}O$; M_r 242.4), of animal or vegetable origin.

Content

— *stearyl alcohol*: minimum 40.0 per cent,

— *sum of the contents of stearyl alcohol and cetyl alcohol*: minimum 90.0 per cent.

CHARACTERS

Appearance

White or pale yellow, wax-like mass, plates, flakes or granules.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent) and in light petroleum. When melted, it is miscible with fatty oils, with liquid paraffin and with melted wool fat.

IDENTIFICATION

Examine the chromatograms obtained in the assay.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the principal peaks in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*). To 0.50 g, add 20 mL of cold *ethanol (96 per cent) R*. Boil until dissolution is complete, then allow to cool.

Melting point (*2.2.14*)

49 °C to 56 °C.

Acid value (*2.5.1*)

Maximum 1.0.

Hydroxyl value (*2.5.3, Method A*)

208 to 228.

Iodine value (*2.5.4, Method A*)

Maximum 2.0.

Dissolve 2.00 g in *methylene chloride R* and dilute to 25 mL with the same solvent.

Saponification value (*2.5.6*)

Maximum 2.0.

ASSAY

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution Dissolve 0.100 g of the substance to be examined in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 60 mg of *cetyl alcohol CRS* and 40 mg of *stearyl alcohol CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 10 mL with *ethanol (96 per cent) R*.

Column:

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *methylpolysiloxane R* (1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Column	0 - 20	150 → 250
	20 - 40	250
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to cetyl alcohol and stearyl alcohol.

Calculate the percentage contents of $C_{16}H_{34}O$ and $C_{18}H_{38}O$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetostearyl Isononanoate

General Notices

(Ph. Eur. monograph 1085)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of esters of cetostearyl alcohol with isononanoic acid, mainly 3,5,5-trimethylhexanoic acid.

CHARACTERS

Appearance

Clear, colourless or slightly yellowish liquid.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent) and in light petroleum, miscible with fatty oils and with liquid paraffins.

Viscosity

15 mPa·s to 30 mPa·s.

Relative density

0.85 to 0.86.

Refractive index

1.44 to 1.45.

IDENTIFICATION

A. On cooling, turbidity occurs below 15 °C.

B. Saponification value (see Tests).

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of cetostearyl isononanoate*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method I*).

Acid value (*2.5.1*)

Maximum 1.0, determined on 5.0 g.

Hydroxyl value (*2.5.3, Method A*)

Maximum 5.0, determined on 4.0 g. Add 5.0 mL of acetylating reagent.

Iodine value (*2.5.4, Method A*)

Maximum 1.0.

Saponification value (*2.5.6*)

135 to 148, determined on 1.0 g.

Water (*2.5.12*)

Maximum 0.2 per cent, determined on 10.0 g.

Total ash (*2.4.16*)

Maximum 0.2 per cent, determined on 2.0 g.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

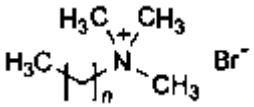
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Cetrimide

General Notices

(Ph. Eur. monograph 0378)



Action and use

Antiseptic.

Preparations

Cetrimide Cream

Cetrimide Emulsifying Ointment

Strong Cetrimide Solution

Ph Eur

DEFINITION

Cetrimide consists of trimethyltetradecylammonium bromide and may contain smaller amounts of dodecyl- and hexadecyl-trimethylammonium bromides.

Content

96.0 per cent to 101.0 per cent of alkyltrimethylammonium bromides, calculated as $C_{17}H_{38}BrN$ (M_r 336.4) (dried substance).

CHARACTERS

Appearance

White or almost white, voluminous, free-flowing powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Dissolve 0.25 g in *alcohol R* and dilute to 25.0 mL with the same solvent. At wavelengths from 260 nm to 280 nm, the absorbance (*2.2.25*) of the solution has a maximum of 0.05.

B. Dissolve about 5 mg in 5 mL of *buffer solution pH 8.0 R*. Add about 10 mg of *potassium ferricyanide R*. A yellow precipitate is formed. Prepare a blank in the same manner but omitting the substance to be examined: a yellow solution is observed but no precipitate is formed.

C. Solution S (see Tests) froths copiously when shaken.

D. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.10 g of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 0.10 g of *trimethyltetradecylammonium bromide CRS* in *water R* and dilute to 5 mL with the same solvent.

Plate *TLC silanised silica gel F_{254} plate R*.

Mobile phase *acetone R*, 270 g/L solution of *sodium acetate R*, *methanol R* (20:35:45 *V/V/V*).

Application 1 µL.

Development Over a path of 12 cm.

Drying In a current of hot air.

Detection Allow to cool; expose the plate to iodine vapour and examine in daylight.

Result The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

E. It gives reaction (a) of bromides (*2.3.1*).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 50 mL of solution S add 0.1 mL of *bromocresol purple solution R*. Not more than 0.1 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Amines and amine salts

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 5.0 g in 30 mL of a mixture of 1 volume of *1 M hydrochloric acid* and 99 volumes of *methanol R* and add 100 mL of *2-propanol R*. Pass a stream of *nitrogen R* slowly through the solution. Gradually add 15.0 mL of *0.1 M tetrabutylammonium hydroxide* and record the potentiometric titration curve (*2.2.20*). If the curve shows 2 points of inflexion, the volume of titrant added between the 2 points is not greater than 2.0 mL.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Dissolve 2.000 g in *water R* and dilute to 100.0 mL with the same solvent. Transfer 25.0 mL of the solution to a separating funnel, add 25 mL of *chloroform R*, 10 mL of *0.1 M sodium hydroxide* and 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R*. Shake, allow to separate and discard the chloroform layer. Shake the aqueous layer with 3 quantities, each of 10 mL, of *chloroform R* and discard the chloroform layers. Add 40 mL of *hydrochloric acid R*, allow to cool and titrate with *0.05 M potassium iodate* until the deep brown colour is almost discharged. Add 2 mL of *chloroform R* and continue the titration, shaking vigorously, until the colour of the chloroform layer no longer changes. Carry out a blank titration on a mixture of 10.0 mL of the freshly prepared 50 g/L solution of *potassium iodide R*, 20 mL of *water R* and 40 mL of *hydrochloric acid R*.

1 mL of *0.05 M potassium iodate* is equivalent to 33.64 mg of $C_{17}H_{38}BrN$.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetrimide Cream

General Notices

Action and use

Antiseptic.

DEFINITION

Cetrimide Cream contains the stated percentage w/w of Cetrimide in a suitable basis.

Extemporaneous preparation

The following formula and directions apply.

Cetrimide	5 g, or a sufficient quantity
Cetostearyl Alcohol	50 g
Liquid Paraffin	500 g
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 g

Melt the Cetostearyl Alcohol and heat with the Liquid Paraffin to about 60°. Dissolve the Cetrimide in sufficient Purified Water to produce about 450 g. Add the aqueous solution to the oily phase when both are at about 60° and mix. Stir gently until cool, add sufficient of the Purified Water to produce 1000 g and mix.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of cetrimide, $C_{17}H_{38}BrN$

88.0 to 106.0% of the stated amount.

IDENTIFICATION

Mix 1 g with 50 mL of *water*. The diluted cream complies with the following tests.

A. To 10 mL add 2 mL of *potassium hexacyanoferrate(III) solution*. A yellow precipitate is produced.

B. Shake 3 mL of *water* with 1 mL of 1M *sulfuric acid*, 2 mL of *chloroform* and 0.5 mL of *methyl orange solution*. Add 2 mL of the diluted cream, shake and allow to separate. A yellow colour develops in the chloroform layer.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

To a quantity containing 5 mg of Cetrimide add 10 mL of hot *water* and shake gently until dispersed. Add 5 mL of 1M *sulfuric acid*, 20 mL of *chloroform* and 0.25 mL of *dimethyl yellow solution* and titrate with 0.001M *dioctyl sodium sulfosuccinate VS*. Each mL of 0.001M *dioctyl sodium sulfosuccinate VS* is equivalent to 0.3364 mg of $C_{17}H_{38}BrN$.

LABELLING

The strength is stated as the percentage w/w of Cetrimide.

When Cetrimide Cream is prescribed or demanded, no strength being stated, a cream containing 0.5% w/w shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetrimide Emulsifying Ointment

General Notices

Action and use

Antiseptic.

DEFINITION

White Soft Paraffin	500 g
Cetostearyl Alcohol	270 g
Liquid Paraffin	200 g
Cetrimide	30 g

Extemporaneous preparation

The following directions apply.

Melt together the White Soft Paraffin, Cetostearyl Alcohol and Liquid Paraffin, add the Cetrimide and stir until cold.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of cetrimide, $C_{17}H_{38}BrN$

2.5 to 3.3% w/w.

ASSAY

To 0.3 g in a stoppered cylinder, add 10 mL of hot *water* and shake until the solid is dispersed. Add 5 mL of 1M *sulfuric acid*, 20 mL of *chloroform* and 1 mL of *dimethyl yellow and oracet blue 2R solution* and titrate with 0.001M *sodium dodecyl sulfate VS*. Each mL of 0.001M *sodium dodecyl sulfate VS* is equivalent to 0.3364 mg of $C_{17}H_{38}BrN$.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetrimide Solution

General Notices

Cetrimide Cutaneous Solution

Sterile Cetrimide Cutaneous Solution

Action and use

Antiseptic.

DEFINITION

Cetrimide Solution is a *cutaneous solution* of cetrimide prepared by appropriately diluting Strong Cetrimide Solution with Purified Water.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of cetrimide, $C_{17}H_{38}BrN$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity containing 100 mg of Cetrimide, add 2 mL of a 5% w/v solution of *potassium hexacyanoferrate(III)*. A yellow precipitate is produced.

B. Shake together 5 mL of *water*, 1 mL of 1M *sulfuric acid*, 2 mL of *chloroform* and 0.05 mL of *methyl orange solution*; the chloroform layer is colourless. Add a quantity of the solution being examined containing 20 mg of Cetrimide and shake. A yellow colour is produced slowly in the chloroform layer.

C. Yields reaction A characteristic *of bromides*, Appendix VI.

ASSAY

To a quantity of the solution containing 1 g of Cetrimide add 25 mL of *chloroform*, 10 mL of 0.1M *sodium hydroxide* and 10 mL of a freshly prepared 8.0% w/v solution of *potassium iodide*. Shake well, allow to separate and discard the chloroform layer. Wash the aqueous layer with three 10-mL quantities of *chloroform* and discard the washings. Add 40 mL of *hydrochloric acid*, cool and titrate with *0.05M potassium iodate VS* until the deep brown colour is almost discharged. Add 2 mL of *chloroform* and continue the titration, with shaking, until the chloroform layer no longer changes colour. Carry out a blank titration on a mixture of 10 mL of the freshly prepared 8.0% w/v potassium iodide solution, 20 mL of *water* and 40 mL of *hydrochloric acid*. The difference between the titrations represents the amount of potassium iodate required. Each mL of *0.05M potassium iodate VS* is equivalent to 0.03364 g of $C_{17}H_{38}BrN$.

STERILE CETRIMIDE SOLUTION

DEFINITION

www.webofpharma.com

https://thuathuocngocanh.com/

DEFINITION

Sterile Cetrimide Solution is Cetrimide Solution that has been sterilised by *heating in an autoclave*.

Content of cetrimide; Identification

Complies with the requirements stated under Cetrimide Solution.

ASSAY

Carry out the Assay described under Cetrimide Solution.

Sterility

Complies with the *test for sterility*, Appendix XVI A.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetyl Alcohol

General Notices

(Ph. Eur. monograph 0540)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of solid alcohols, mainly hexadecan-1-ol ($C_{16}H_{34}O$; M_r 242.4), of animal or vegetable origin.

Content

Minimum 95.0 per cent of $C_{16}H_{34}O$.

CHARACTERS

Appearance

White or almost white, unctuous mass, powder, flakes or granules.

Solubility

Practically insoluble in water, freely soluble or sparingly soluble in ethanol (96 per cent). When melted, it is miscible with vegetable and animal oils, with liquid paraffin and with melted wool fat.

IDENTIFICATION

Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 (*2.2.2, Method II*).

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.50 g in 20 mL of boiling *ethanol (96 per cent) R*. Allow to cool.

Melting point (*2.2.14*)

46 °C to 52 °C.

Acid value (*2.5.1*)

Maximum 1.0.

Hydroxyl value (*2.5.3, Method A*)

218 to 238.

Iodine value (*2.5.4, Method A*)

Maximum 2.0.

Dissolve 2.00 g in *methylene chloride R* and dilute to 25 mL with the same solvent.

Saponification value (*2.5.6*)

Maximum 2.0.

ASSAY

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution Dissolve 0.100 g of the substance to be examined in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of *cetyl alcohol CRS* in *ethanol (96 per cent) R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 50 mg of *stearyl alcohol R* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Reference solution (c) Mix 1 mL of reference solution (a) and 1 mL of reference solution (b) and dilute to 10 mL with *ethanol (96 per cent) R*.

Column:

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *methylpolysiloxane R* (1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Column	0 - 20	150 → 250
	20 - 40	250
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL of the test solution and reference solutions (a) and (c).

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to cetyl alcohol and stearyl alcohol.

Calculate the percentage content of $C_{16}H_{34}O$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cetyl Palmitate

General Notices

(Ph. Eur. monograph 1906)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of esters of C_{14}-C_{18} alcohols with lauric (dodecanoic), myristic (tetradecanoic), palmitic (hexadecanoic) and stearic (octadecanoic) acids (‘Cetyl esters wax').

Content

(expressed as hexadecyl hexadecanoate):

10.0 per cent to 20.0 per cent for Cetyl palmitate 15, 60.0 per cent to 70.0 per cent for Cetyl palmitate 65 and minimum 90.0 per cent for Cetyl palmitate 95.

CHARACTERS

Appearance

White or almost white, waxy plates, flakes or powder.

Solubility

Practically insoluble in water, soluble in boiling anhydrous ethanol and in methylene chloride, slightly soluble in light petroleum, practically insoluble in anhydrous ethanol.

mp

About 45 °C for Cetyl palmitate 15 and Cetyl palmitate 65 and about 52 °C for Cetyl palmitate 95.

IDENTIFICATION

A. It complies with the limits of the assay and the chromatogram obtained with the test solution shows the typical main peak(s).

B. Saponification value (see Tests).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

The solution is not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 4.0 g in *methylene chloride R* and dilute to 20 mL with the same solvent.

Acid value (*2.5.1*)

Maximum 4.0.

Dissolve 10.0 g in 50 mL of the solvent mixture described by heating under reflux on a water-bath for 5 min.

Hydroxyl value (*2.5.3, Method A*)

Maximum 20.0.

Carry out the titration at a temperature between 55 °C and 70 °C, shaking the flask towards the end of the titration.

Iodine value (*2.5.4, Method A*)

Maximum 2.0.

Saponification value (*2.5.6*)

105 to 120.

Heat under reflux for 2 h.

Alkaline impurities

Dissolve 2.0 g with gentle heating in a mixture of 1.5 mL of *ethanol (96 per cent) R* and 3 mL of *toluene R*. Add 0.05 mL of a 0.4 g/L solution of *bromophenol blue R* in *ethanol (96 per cent) R*. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the solution to yellow.

Water (*2.5.12*)

Maximum 0.3 per cent, determined on 1.0 g using a mixture of equal volumes of *anhydrous methanol R* and *methylene chloride R* as solvent.

Total ash (*2.4.16*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution Dissolve 20.0 mg of the substance to be examined in *hexane R* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 20.0 mg of *cetyl palmitate 95 CRS* in *hexane R* and dilute to 20.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 20.0 mg of *cetyl palmitate 15 CRS* in *hexane R* and dilute to 20.0 mL with the same solvent.

Column:

— *material*: stainless steel;

— *size*: *l* = 10 m, Ø = 0.53 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 2.65 µm).

Carrier gas *helium for chromatography R*.

Flow rate 6.5 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	100 → 300
	10 - 15	300
Injection port		350
Detector		350

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to cetyl palmitate (retention time = about 9 min): cetyl alcohol = about 0.3; palmitic acid = about 0.4; lauric ester = about 0.8; myristic ester = about 0.9; stearic ester = about 1.1.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to cetyl palmitate and cetyl stearate.

STORAGE

At a temperature not exceeding 25 °C.

LABELLING

The label states the type of cetyl palmitate.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

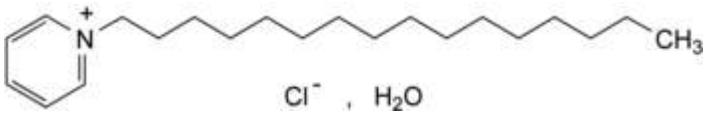
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Cetylpyridinium Chloride

General Notices

(Ph. Eur. monograph 0379)



$C_{21}H_{38}ClN,H_2O$ 358.0 *6004-24-6*

Action and use

Antiseptic.

Ph Eur

DEFINITION

Cetylpyridinium chloride contains not less than 96.0 per cent and not more than the equivalent of 101.0 per cent of 1-hexadecylpyridinium chloride, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white powder, slightly soapy to the touch, soluble in water and in ethanol (96 per cent). An aqueous solution froths copiously when shaken.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Dissolve 0.10 g in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *water R*. Examined between 240 nm and 300 nm (*2.2.25*), the solution shows an absorption maximum at 259 nm and 2 shoulders at about 254 nm and at about 265 nm. The specific absorbance at the maximum is 126 to 134, calculated with reference to the anhydrous substance.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *cetylpyridinium chloride CRS*. Examine the substances in the solid state.

www.webofpharma.com

https://thuocngocanh.com/

C. To 5 mL of *dilute sodium hydroxide solution R* add 0.1 mL of *bromophenol blue solution R1* and 5 mL of *chloroform R* and shake. The chloroform layer is colourless. Add 0.1 mL of solution S (see Tests) and shake. The chloroform layer becomes blue.

D. Solution S gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and is colourless (*2.2.2, Method II*).

Acidity

To 50 mL of solution S add 0.1 mL of *phenolphthalein solution R*. Not more than 2.5 mL of *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Amines and amine salts

Dissolve 5.0 g with heating in 20 mL of a mixture of 3 volumes of *1 M hydrochloric acid* and 97 volumes of *methanol R* and add 100 mL of *2-propanol R*. Pass a stream of *nitrogen R* slowly through the solution. Gradually add 12.0 mL of *0.1 M tetrabutylammonium hydroxide* and record the potentiometric titration curve (*2.2.20*). If the curve shows 2 points of inflexion, the volume of titrant added between the two points is not greater than 5.0 mL. If the curve shows no point of inflexion, the substance to be examined does not comply with the test. If the curve shows one point of inflexion, repeat the test but add 3.0 mL of a 25.0 g/L solution of *dimethyldecylamine R* in *2-propanol R* before the titration. If the titration curve after the addition of 12.0 mL of the titrant shows only one point of inflexion, the substance to be examined does not comply with the test.

Water (*2.5.12*)

4.5 per cent to 5.5 per cent, determined on 0.300 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Not more than 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 2.00 g in *water R* and dilute to 100.0 mL with the same solvent. Transfer 25.0 mL of the solution to a separating funnel, add 25 mL of *chloroform R*, 10 mL of *0.1 M sodium hydroxide* and 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R*. Shake well, allow to separate and discard the chloroform layer. Shake the aqueous layer with three quantities, each of 10 mL, of *chloroform R* and discard the chloroform layers. To the aqueous layer add 40 mL of *hydrochloric acid R*, allow to cool and titrate with *0.05 M potassium iodate* until the deep-brown colour is almost discharged. Add 2 mL of *chloroform R* and continue the titration, shaking vigorously, until the chloroform layer no longer changes colour. Carry out a blank titration on a mixture of 10.0 mL of the freshly prepared 50 g/L solution of *potassium iodide R*, 20 mL of *water R* and 40 mL of *hydrochloric acid R*.

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *0.05 M potassium iodate* is equivalent to 34.0 mg of $C_{21}H_{38}ClN$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chalk

General Notices

Prepared Chalk

$CaCO_3$ 100.1

Action and use

Antacid.

DEFINITION

Chalk is a native form of calcium carbonate freed from most of its impurities by elutriation and dried. It contains not less than 97.0% and not more than 100.5% of $CaCO_3$, calculated with reference to the dried substance.

CHARACTERISTICS

Chalk absorbs water readily.

Practically insoluble in *water*; slightly soluble in *water* containing carbon dioxide.

Macroscopical White or greyish white, small friable masses, usually conical in form, or in powder; amorphous; earthy; soft to the touch.

Microscopical Consists of the calcareous shells and detritus of various foraminifera; the calcareous shells vary from about 35 to 100 µm in breadth and from about 50 to 180 µm in length; among the detritus are numerous small rings and discs about 5 to 10 µm in diameter.

IDENTIFICATION

A. A solution in 6M *acetic acid* yields reaction C characteristic of *calcium salts*, Appendix VI.

B. Yields reaction A characteristic of *carbonates*, Appendix VI.

TESTS

Acidity or alkalinity

1 g, boiled with 50 mL of *water* and filtered, yields a filtrate which is neutral to *bromothymol blue solution R3* or requires not more than 0.05 mL of *0.1M hydrochloric acid VS* to make it so.

Aluminium, iron, phosphate and matter insoluble in hydrochloric acid

Dissolve 2 g in a mixture of 5 mL of *hydrochloric acid* and 75 mL of *water*, boil to remove carbon dioxide and make alkaline with 5M *ammonia* using *methyl red solution* as indicator. Boil for 1 minute, filter and wash the precipitate with a hot 2% w/v solution of *ammonium*

www.webofpharma.com

https://thuocngocanh.com/

chloride. Dissolve the precipitate as completely as possible by passing 20 mL of hot *2M hydrochloric acid* through the filter and wash the filter with sufficient hot *water* to adjust the volume of the solution to 50 mL. Boil the solution and make alkaline with 5M *ammonia* using *methyl red solution* as indicator. Boil for 1 minute, filter through the same filter, wash the precipitate with a hot 2% w/v solution of *ammonium nitrate*, dry and ignite at a temperature not lower than 1000°. The residue weighs not more than 40 mg.

Arsenic

Dissolve 0.5 g in 5 mL of *brominated hydrochloric acid* and dilute to 50 mL with *water*. 25 mL of the resulting solution complies with the *limit test for arsenic*, Appendix VII (4 ppm).

Chloride

Dissolve 0.3 g in 2 mL of *nitric acid* and 10 mL of *water*, filter and dilute the filtrate to 30 mL with *water*. 15 mL of the resulting solution complies with the *limit test for chlorides*, Appendix VII (330 ppm).

Sulfate

Dissolve 0.25 g in 5.5 mL of *2M hydrochloric acid*, dilute to 30 mL with *water* and filter. 15 mL of the resulting solution complies with the *limit test for sulfates*, Appendix VII (0.12%).

Loss on drying

When dried to constant weight at 105°, loses not more than 1.0% of its weight. Use 1 g.

ASSAY

To 2 g in 100 mL of *water* add 50 mL of *1M hydrochloric acid VS*, boil to remove carbon dioxide, cool and titrate the excess of acid with *1M sodium hydroxide VS* using *methyl orange solution* as indicator. Each mL of *1M hydrochloric acid VS* is equivalent to 50.04 mg of $CaCO_3$.

© Crown Copyright 2022

www.webofpharma.com

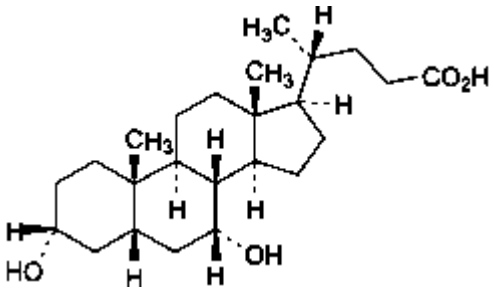
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chenodeoxycholic Acid

General Notices

(Ph. Eur. monograph 1189)



$C_{24}H_{40}O_4$ 392.6 *474-25-9*

Action and use

Bile acid; treatment of gallstones.

Ph Eur

DEFINITION

3α,7α-Dihydroxy-5β-cholan-24-oic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent), soluble in acetone, slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *chenodeoxycholic acid CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Solvent mixture *water R*, *acetone R* (10:90 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution Dissolve 20 mg of *chenodeoxycholic acid CRS* in the solvent mixture and dilute to 5 mL with the solvent mixture.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *methylene chloride R* (1:30:60 *V/V/V*).

Application 5 µL.

Development In an unsaturated tank, over 2/3 of the plate.

Drying At 120 °C for 10 min.

Detection Spray immediately with a 47.6 g/L solution of *phosphomolybdic acid R* in a mixture of 1 volume of *sulfuric acid R* and 20 volumes of *glacial acetic acid R* and heat the plate at 120 °C until blue spots appear.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve about 10 mg in 1 mL of *sulfuric acid R*. Add 0.1 mL of *formaldehyde solution R* and allow to stand for 5 min. Add 5 mL of *water R*. The suspension obtained is greenish-blue.

TESTS

Specific optical rotation (2.2.7)

+ 11.0 to + 13.0 (dried substance).

Dissolve 0.500 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Impurity I

Liquid chromatography (2.2.29).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 0.4 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 40 mg of *chenodeoxycholic acid for system suitability CRS* (containing impurity I) in 1 mL of *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase *phosphoric acid R*, 6.8 g/L solution of *potassium dihydrogen phosphate R*, *acetonitrile R* (0.1:45:55 *V/V/V*).

Flow rate 1.5 mL/min.

Detection Differential refractometer maintained at 40 °C.

Injection 15 µL.

Run time 13 times the retention time of chenodeoxycholic acid.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity I.

Relative retention With reference to chenodeoxycholic acid (retention time = about 2 min): impurity I = about 10.

System suitability Reference solution (b):

— *resolution*: minimum 20 between the peaks due to chenodeoxycholic acid and impurity I.

Calculation of percentage content:

— for impurity I, use the concentration of chenodeoxycholic acid in reference solution (a).

Limit:

— *impurity I*: maximum 0.5 per cent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.5 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 4 mg of *ursodeoxycholic acid CRS* (impurity A) and 4 mg of *cholic acid CRS* (impurity B) in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (c) Dissolve 40 mg of *chenodeoxycholic acid for peak identification CRS* (containing impurity H) in 1 mL of *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase *phosphoric acid R*, *acetonitrile R*, 6.8 g/L solution of *potassium dihydrogen phosphate R* (0.1:40:60 *V/V/V*).

Flow rate 1.5 mL/min.

Detection Differential refractometer maintained at 40 °C.

Injection 15 µL.

Run time 4 times the retention time of chenodeoxycholic acid.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity H.

Relative retention With reference to chenodeoxycholic acid (retention time = about 5.7 min): impurity H = about 0.35; impurity B = about 0.45; impurity A = about 0.5.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and A.

Calculation of percentage contents:

— for each impurity, use the concentration of chenodeoxycholic acid in reference solution (a).

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurity H*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent.

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Maximum 1.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

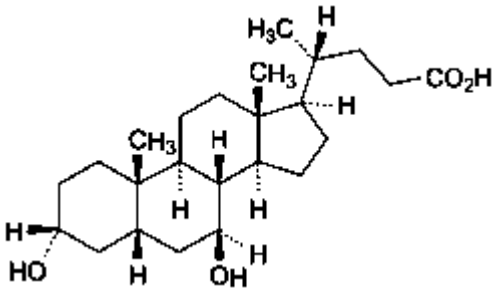
Dissolve 0.350 g in 50 mL of *ethanol (96 per cent) R*. Add 50 mL of *water R* and titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 39.26 mg of $C_{24}H_{40}O_4$.

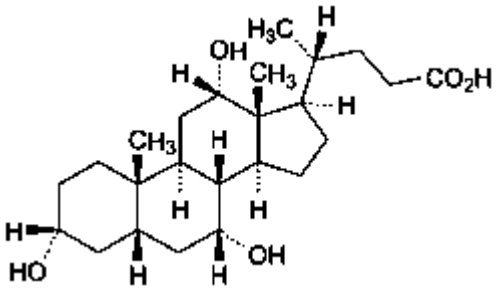
IMPURITIES

Specified impurities *B, H, I.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, F, G.*



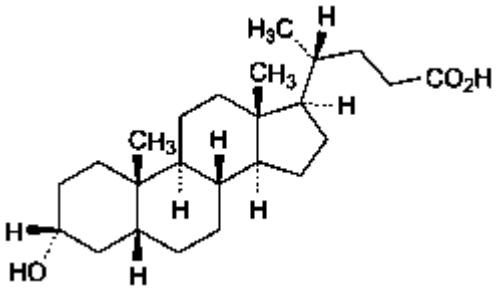
A. 3α-7β-dihydroxy-5β-cholan-24-oic acid (ursodeoxycholic acid),



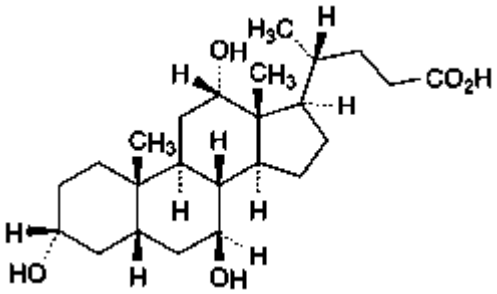
B. 3α,7α,12α-trihydroxy-5β-cholan-24-oic acid (cholic acid),

www.webofpharma.com

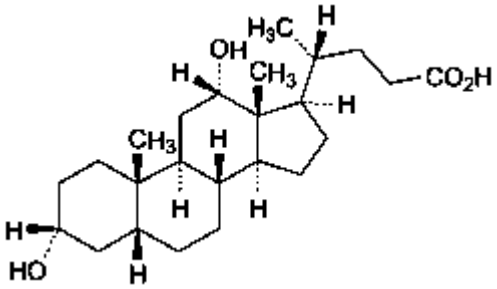
https://thuocngocanh.com/



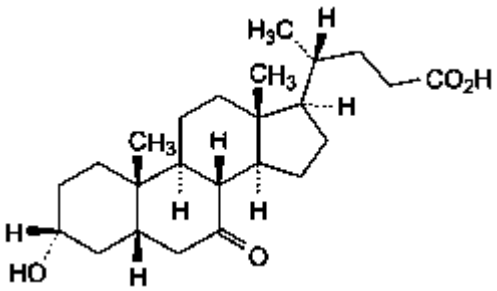
C. 3α-hydroxy-5β-cholan-24-oic acid (lithocholic acid),



D. 3α,7β,12α-trihydroxy-5β-cholan-24-oic acid (ursocholic acid),



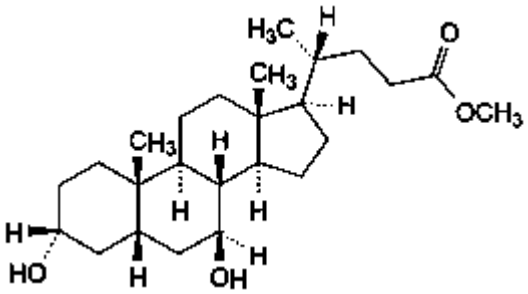
E. 3α,12α-dihydroxy-5β-cholan-24-oic acid (deoxycholic acid),



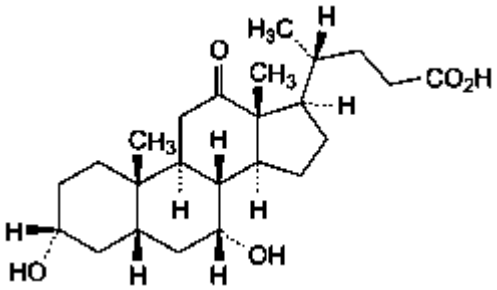
F. 3α-hydroxy-7-oxo-5β-cholan-24-oic acid,

www.webofpharma.com

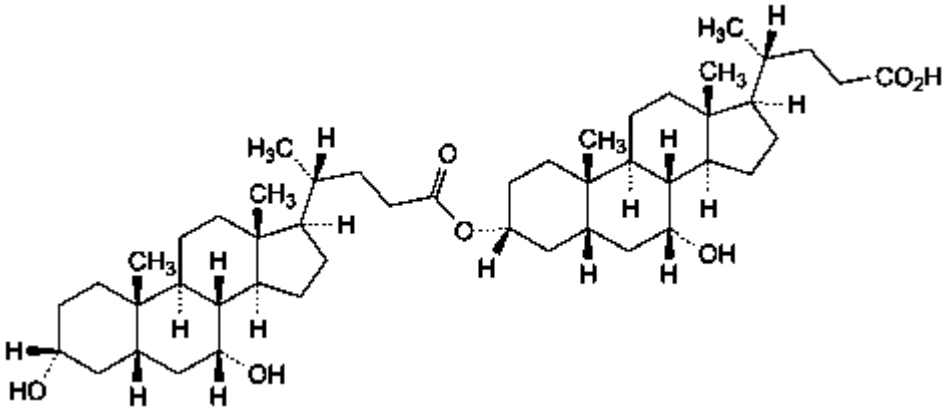
https://thuocngocanh.com/



G. methyl 3α,7β-dihydroxy-5β-cholan-24-oate,



H. 3α,7α-dihydroxy-12-oxo-5β-cholan-24-oic acid,



I. 3α-[(3α,7α-dihydroxy-24-oxo-5β-cholan-24-yl)oxy]-7α-hydroxy-5β-cholan-24-oic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chitosan Hydrochloride

General Notices

(Ph. Eur. monograph 1774)

Ph Eur

DEFINITION

Chitosan hydrochloride is the chloride salt of an unbranched binary heteropolysaccharide consisting of the two units *N*-acetyl-D-glucosamine and D-glucosamine, obtained by partial deacetylation of chitin normally leading to a degree of deacetylation of 70.0 per cent to 95.0 per cent. Chitin is extracted from the shells of shrimp and crab.

PRODUCTION

The animals from which chitosan hydrochloride is derived must fulfil the requirements for the health of animals suitable for human consumption to the satisfaction of the competent authority. It must have been shown to what extent the method of production allows inactivation or removal of any contamination by viruses or other infectious agents.

CHARACTERS

Appearance

White or almost white, fine powder.

Solubility

Sparingly soluble in water, practically insoluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Comparison *chitosan hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

C. Dilute 50 mL of solution S (see Tests) to 250 mL with a 25 per cent *V/V* solution of *ammonia R*. A voluminous gelatinous mass is formed.

D. To 10 mL of solution S add 90 mL of *acetone R*. A voluminous gelatinous mass is formed.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 1.0 g in 100 mL of *water R* and stir vigorously for 20 min with a mechanical stirrer.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Matter insoluble in water

Maximum 0.5 per cent.

Add 2.00 g to 400.0 mL of *water R* while stirring until no further dissolution takes place. Transfer the solution to a 2 L beaker, and add 200 mL of *water R*. Boil the solution gently for 2 h, covering the beaker during the operation. Filter through a sintered-glass filter (40) (*2.1.2*), wash the residue with water and dry to constant weight in an oven at 100-105 °C. The residue weighs a maximum of 10 mg.

pH (*2.2.3*)

4.0 to 6.0 for solution S.

Viscosity (*2.2.10*)

80 per cent to 120 per cent of the value stated on the label, determined on solution S.

Determine the viscosity using a rotating viscometer at 20 °C with a spindle rotating at 20 r/min, using a suitable spindle for the range of the expected viscosity.

Degree of deacetylation

Test solution Dissolve 0.250 g in *water R* and dilute to 50.0 mL with the same solvent, stirring vigorously. Dilute 1.0 mL of this solution to 100.0 mL with *water R*. Measure the absorbance (*2.2.25*) from 200 nm to 205 nm as the first derivative of the absorbance curve. Determine the pH of the solution.

Reference solutions Prepare solutions of 1.0 µg/mL, 5.0 µg/mL, 15.0 µg/mL and 35.0 µg/mL of *N-acetylglucosamine R* in *water R*. Measure the absorbance (*2.2.25*) from 200 nm to 205 nm of each solution as the first derivative of the absorption curve. Make a standard curve by plotting the first derivative at 202 nm as a function of the concentration of *N*-acetylglucosamine, and calculate the slope of the curve by least squares linear regression. Use the standard curve to determine the equivalent amount of *N*-acetylglucosamine for the substance to be examined.

Calculate the degree of deacetylation (molar) using the following expression:

$$\frac{100 \times M_1 \times \left(C_1 - C_2 \right)}{\left(M_1 \times C_1 \right) - \left[\left(M_1 - M_3 \right) \times C_2 \right]}$$

C_1 = concentration of chitosan hydrochloride in the test solution in micrograms per millilitre;

www.webofpharma.com

https://thuocngocanh.com/

C_2 = concentration of *N*-acetylglucosamine in the test solution, as determined from the standard curve prepared using the reference solution in micrograms per millilitre;

M_1 = 203 (relative molecular mass of *N*-acetylglucosamine unit ($C_8H_{13}NO_5$) in polymer);

M_3 = relative molecular mass of chitosan hydrochloride.

M_3 is calculated from the pH in solution, assuming a pKa value of 6.8, using the following equations:

$$M_3 = f \times M_2 + (1 - f) \times \left(M_2 + 36.5 \right)$$

$$f = \frac{p}{1+p}$$

$$p = 10^{(\mathrm{pH} - \mathrm{pKa})}$$

M_2 = 161 (relative molecular mass of deacetylated unit (glucosamine) ($C_6H_{11}NO_4$) in polymer).

Chlorides

10.0 per cent to 20.0 per cent.

Introduce 0.200 g into a 250 mL borosilicate flask fitted with a reflux condenser. Add 40 mL of a mixture of 1 volume of *nitric acid R* and 2 volumes of *water R*. Boil gently under a reflux condenser for 5 min. Cool and add 25 mL of *water R* through the condenser. Add 16.0 mL of *0.1 M silver nitrate*, shake vigorously and titrate with *0.1 M ammonium thiocyanate*, using 1 mL of *ferric ammonium sulfate solution R2* as indicator, and shaking vigorously towards the end-point. Carry out a blank titration.

1 mL of *0.1 M silver nitrate* is equivalent to 3.55 mg of Cl.

Loss on drying (*2.2.32*)

Maximum 10 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 1.0 g.

STORAGE

At a temperature of 2 °C to 8 °C, protected from moisture and light.

LABELLING

The label states the nominal viscosity in millipascal seconds for a 10 g/L solution in *water R*.

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

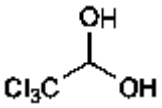
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Chloral Hydrate

General Notices

(Ph. Eur. monograph 0265)



$C_2H_3Cl_3O_2$ 165.4 *302-17-0*

Action and use

Hypnotic.

Preparation

Chloral Hydrate Oral Solution

Ph Eur

DEFINITION

2,2,2-Trichloroethane-1,1-diol.

Content

98.5 per cent to 101.0 per cent.

CHARACTERS

Appearance

Colourless, transparent crystals.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. To 10 mL of solution S (see Tests) add 2 mL of *dilute sodium hydroxide solution R*. The mixture becomes cloudy and, when heated, gives off an odour of chloroform.

B. To 1 mL of solution S add 2 mL of *sodium sulfide solution R*. A yellow colour develops which quickly becomes reddish-brown. On standing for a short time, a red precipitate may be formed.

TESTS

Solution S

Dissolve 3.0 g in *carbon dioxide-free water R* and dilute to 30 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

3.5 to 5.5 for solution S.

Chloral alcoholate

Warm 1.0 g with 10 mL of *dilute sodium hydroxide solution R*, filter the supernatant and add *0.05 M iodine* dropwise until a yellow colour is obtained. Allow to stand for 1 h. No precipitate is formed.

Chlorides (*2.4.4*)

Maximum 100 ppm.

Dilute 5 mL of solution S to 15 mL with *water R*.

Non-volatile residue

Maximum 0.1 per cent.

Evaporate 2.000 g on a water-bath. The residue weighs a maximum of 2 mg.

ASSAY

Dissolve 4.000 g in 10 mL of *water R* and add 40.0 mL of *1 M sodium hydroxide*. Allow to stand for exactly 2 min and titrate with *0.5 M sulfuric acid*, using 0.1 mL of *phenolphthalein solution R* as indicator. Titrate the neutralised solution with *0.1 M silver nitrate*, using 0.2 mL of *potassium chromate solution R* as indicator. Calculate the number of millilitres of *1 M sodium hydroxide* used by deducting from the volume of *1 M sodium hydroxide*, added at the beginning of the titration, the volume of *0.5 M sulfuric acid* used in the 1st titration and two-fifteenths of the volume of *0.1 M silver nitrate* used in the 2nd titration.

1 mL of *1 M sodium hydroxide* is equivalent to 0.1654 g of $C_2H_3Cl_3O_2$.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloral Hydrate Oral Solution

General Notices

Action and use

Hypnotic.

DEFINITION

Chloral Hydrate Oral Solution is a solution of Chloral Hydrate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of chloral hydrate, $C_2H_3Cl_3O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To 1 mL of the oral solution add 2 mL of *sodium sulfide solution*; a yellow colour is produced which quickly becomes reddish-brown. On standing for a short time a red precipitate may be formed.

B. Dilute a quantity of the oral solution with sufficient *water* to produce a solution containing 0.01% w/v of Chloral Hydrate. To 10 mL of this solution add 10 mL of a 1.5% w/v solution of *1-ethylquinaldinium iodide* which has been filtered through a 0.45-µm filter; add 60 mL of *propan-2-ol*, 5 mL of 0.1M *ethanolamine* and 15 mL of *water*. Mix and heat in a water bath at 60° for 15 minutes; a blue colour is produced.

ASSAY

To a weighed quantity of the oral solution containing 0.125 g of Chloral Hydrate add 2.5 g of *zinc powder*, 15 mL of *glacial acetic acid* and 30 mL of *water*. Boil under a reflux condenser for 30 minutes, cool, filter through absorbent cotton and wash the residue with *water*. Combine the filtrate and washings, add 20 mL of 2M *nitric acid* and 30 mL of 0.1M *silver nitrate VS*, shake vigorously and filter. Wash the residue with *water* and titrate the excess of silver nitrate in the combined filtrate and washings with *0.1M ammonium thiocyanate VS* using *ammonium iron(III) sulfate solution R2* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 5.513 mg of $C_2H_3Cl_3O_2$. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_2H_3Cl_3O_2$, weight in volume.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

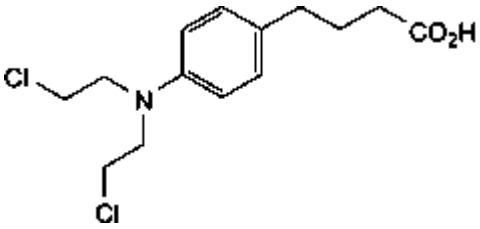
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorambucil

General Notices

(Ph. Eur. monograph 0137)



$C_{14}H_{19}Cl_2NO_2$ 304.2 *305-03-3*

Action and use

Cytotoxic alkylating agent.

Preparation

Chlorambucil Tablets

Ph Eur

DEFINITION

4-[4-[Bis(2-chloroethyl)amino]phenyl]butanoic acid.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison chlorambucil CRS.

TESTS

Impurity G

Liquid chromatography (2.2.29). *The solutions are stable for 8 h at room temperature or for 24 h at 4-8 °C; protect them from light.*

Test solution Dissolve 10 mg of the substance to be examined in methanol R and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of chlorambucil with impurity G CRS in methanol R and dilute to 10.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: phenylsilyl silica gel for chromatography R (5 µm).

Mobile phase methanol R, 1 per cent *V/V* solution of trifluoroacetic acid R (50:50 *V/V*).

Flow rate 1.8 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL.

Run time Twice the retention time of chlorambucil.

Relative retention With reference to chlorambucil (retention time = about 11 min): impurity G = about 1.2.

System suitability Reference solution (b):

— resolution: minimum 1.5 between the peaks due to chlorambucil and impurity G.

Limit:

— *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Solvent mixture 10.3 g/L solution of hydrochloric acid R, acetonitrile for chromatography R (10:90 *V/V*).

Test solution Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *chlorambucil for system suitability CRS* (containing impurities B and E) in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 1.9 g/L solution of *ammonium acetate R* adjusted to pH 3.9 with *acetic acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	60	40
5 - 15	60 → 10	40 → 90
15 - 25	10	90

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *chlorambucil for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and E.

Relative retention With reference to chlorambucil (retention time = about 12 min): impurity B = about 0.5; impurity E = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity B and chlorambucil.

Limits:

— *impurity E*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *impurity B*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 10 mL of *acetone R* and add 10 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, using 0.1 mL of *phenolphthalein solution R* as indicator.

1 mL of *0.1 M sodium hydroxide* is equivalent to 30.42 mg of $C_{14}H_{19}Cl_2NO_2$.

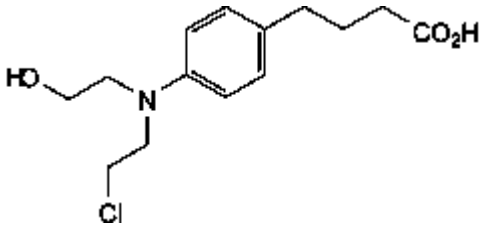
STORAGE

Protected from light.

IMPURITIES

Specified impurities B, E, G.

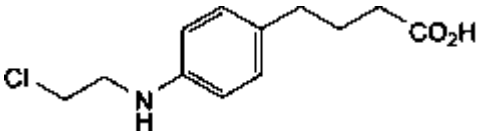
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D, F.



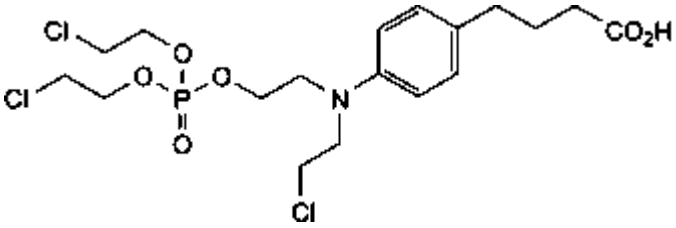
A. 4-[4-[(2-chloroethyl)(2-hydroxyethyl)amino]phenyl]butanoic acid,

www.webofpharma.com

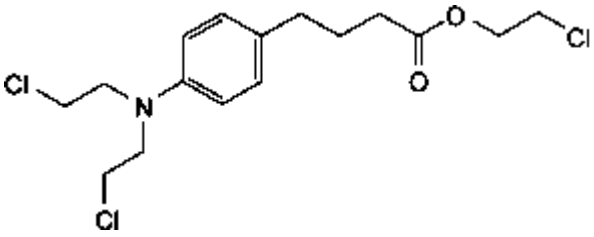
https://thuocngocanh.com/



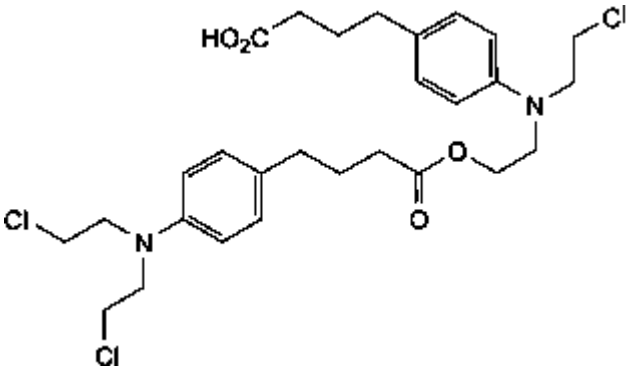
B. 4-[4-[(2-chloroethyl)amino]phenyl]butanoic acid,



C. 4-[4-[[2-[[bis(2-chloroethoxy)phosphoryl]oxy]ethyl](2-chloroethyl)amino]phenyl]butanoic acid,



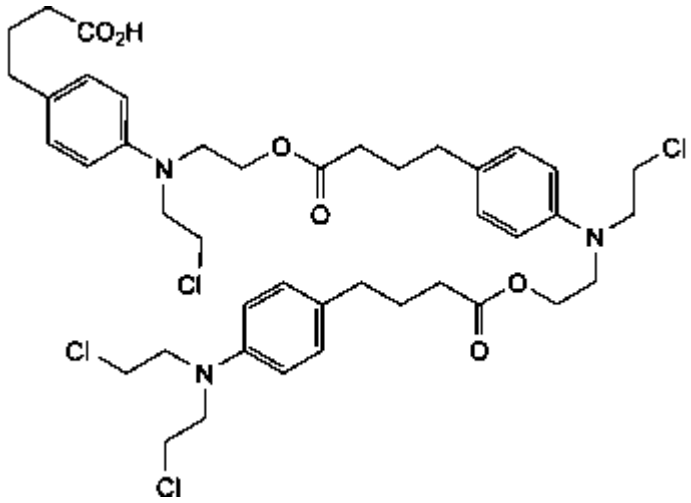
D. 2-chloroethyl 4-[4-[bis(2-chloroethyl)amino]phenyl]butanoate,



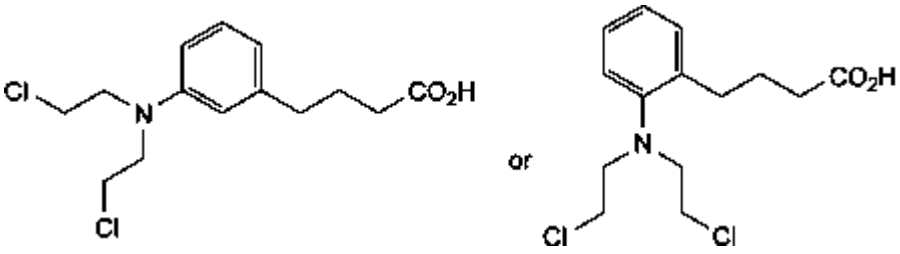
E. 4-[4-[[2-[[4-[4-[bis(2-chloroethyl)amino]phenyl]butanoyl]oxy]ethyl](2-chloroethyl)amino]phenyl]butanoic acid,

www.webofpharma.com

https://thuocngocanh.com/



F. 4-[4-[[2-[[4-[4-[[2-[[4-[4-[bis(2-chloroethyl)amino]phenyl]butanoyl]oxy]ethyl](2-chloroethyl)amino]phenyl]butanoyl]oxy]ethyl](2-chloroethyl)amino]phenyl]butanoic acid,



G. 4-[2-[bis(2-chloroethyl)amino]phenyl]butanoic acid or 4-[3-[bis(2-chloroethyl)amino]phenyl]butanoic acid (*meta* or *ortho* chlorambucil).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorambucil Tablets

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Chlorambucil Tablets contain Chlorambucil. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of chlorambucil, $C_{14}H_{19}Cl_2NO_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 10 mg of Chlorambucil with 10 mL of 2M *hydrochloric acid*, allow to stand for 30 minutes, shaking occasionally, and filter. To 5 mL of the filtrate add 0.5 mL of *potassium tetraiodomercurate solution*; a precipitate is produced. To the remainder of the filtrate add 0.15 mL of *dilute potassium permanganate solution*; the colour of the permanganate is discharged.

TESTS

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Chlorambucil comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve one tablet as completely as possible in 10 mL of 0.1M *hydrochloric acid*, add 40 mL of *acetonitrile* and mix for 5 minutes with the aid of ultrasound. Add sufficient *acetonitrile* to produce a solution containing 0.002% w/v of chlorambucil, filter through a glass microfibre filter (Whatman GF/C is suitable), discarding the first 20 mL of filtrate, and use the filtrate.

(2) 0.0020% w/v of *chlorambucil BPCRS* in a mixture of 1 volume of 0.1M *hydrochloric acid* and 9 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

www.webofpharma.com

https://thuvienthuocngocanh.com/

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of 0.02M *potassium dihydrogen orthophosphate* and 60 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{19}Cl_2NO_2$ in the tablet using the declared content of $C_{14}H_{19}Cl_2NO_2$ in *chlorambucil BPCRS*.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve as completely as possible a quantity of the powdered tablets containing 10 mg of Chlorambucil in a mixture of 25 mL of 0.1M *hydrochloric acid* and 100 mL of *acetonitrile* by mixing for 10 minutes with the aid of ultrasound. Dilute to 250 mL with *acetonitrile*, filter through a glass microfibre filter (Whatman GF/C is suitable), discarding the first 20 mL of filtrate, and dilute 50 mL to 100 mL with a mixture of 1 volume of 0.1M *hydrochloric acid* and 9 volumes of *acetonitrile*.

(2) 0.0020% w/v of *chlorambucil BPCRS* in a mixture of 1 volume of 0.1M *hydrochloric acid* and 9 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{19}Cl_2NO_2$ in the tablets using the declared content of $C_{14}H_{19}Cl_2NO_2$ in *chlorambucil BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

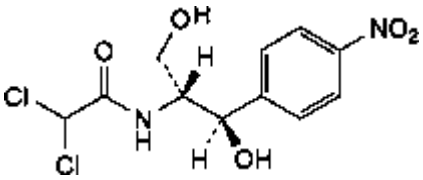
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloramphenicol

General Notices

(Ph. Eur. monograph 0071)



$C_{11}H_{12}Cl_2N_2O_5$ 323.1 *56-75-7*

Action and use

Antibacterial.

Preparations

Chloramphenicol Capsules

Chloramphenicol Ear Drops

Chloramphenicol Eye Drops

Chloramphenicol Eye Ointment

Ph Eur

DEFINITION

2,2-Dichloro-*N*-[(1*R*,2*R*)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White, greyish-white or yellowish-white, fine, crystalline powder or fine crystals, needles or elongated plates.

Solubility

www.webofpharma.com

https://thuvienthuocngocanh.com/

Slightly soluble in water, freely soluble in ethanol (96 per cent) and in propylene glycol.

A solution in anhydrous ethanol is dextrorotatory and a solution in ethyl acetate is laevorotatory.

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *chloramphenicol CRS*.

B. Melting point (2.2.14).

Determination A Determine the melting point of the substance to be examined.

Results A 149 °C to 153 °C.

Determination B Mix equal parts of the substance to be examined and *chloramphenicol CRS* and determine the melting point of the mixture.

Results B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

TESTS

Acidity or alkalinity

To 0.1 g add 20 mL of *carbon dioxide-free water R*, shake and add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.1 mL of *0.02 M hydrochloric acid* or *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Specific optical rotation (2.2.7)

+ 18.5 to + 20.5.

Dissolve 1.50 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solution A Dissolve 2.0 g of *sodium heptanesulfonate R* in 900 mL of *water for chromatography R*. Add 6.8 g of *potassium dihydrogen phosphate R* and 5 mL of *triethylamine R*. Adjust to pH 2.5 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution (a) Dissolve 20.0 mg of the substance to be examined in 10 mL of *methanol R* and dilute to 200.0 mL with mobile phase A.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 50.0 mL with mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 20.0 mg of *chloramphenicol CRS* in 10 mL of *methanol R* and dilute to 200.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of test solution (b) to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 12.5 mg of *4-nitrobenzaldehyde R* (impurity B) in 2 mL of *methanol R* and dilute to 50 mL with mobile phase A.

Reference solution (d) Dissolve 5 mg of *chloramphenicol for peak identification CRS* (containing impurity A) in 1 mL of *methanol R*, add 1 mL of reference solution (c) and dilute to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, solution A (32:68 *V/V*);

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 13	100	0
13 - 25	100 → 60	0 → 40
25 - 33	60	40

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 277 nm.

Injection 10 µL of test solution (b) and reference solutions (b) and (d).

Identification of impurities Use the chromatogram supplied with *chloramphenicol for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A and B.

Relative retention With reference to chloramphenicol (retention time = about 14 min): impurity A = about 0.7; impurity B = about 0.9.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to impurity B and chloramphenicol.

www.webofpharma.com

https://thuocngocanh.com/

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.7;

— for each impurity, use the concentration of chloramphenicol in reference solution (b).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (*2.4.4*)

Maximum 100 ppm.

To 1.00 g add 10 mL of *nitric acid R* and 20 mL of *water R* and shake for 5 min. Filter through a filter paper previously washed by filtering 5 mL portions of *water R* until 5 mL of filtrate no longer becomes opalescent on addition of 0.1 mL of *nitric acid R* and 0.1 mL of *silver nitrate solution R1*. 15 mL of the filtrate complies with the test.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase A.

Injection Test solution (a) and reference solution (a).

Run time 1.5 times the retention time of chloramphenicol.

Calculate the percentage content of $C_{11}H_{12}Cl_2N_2O_5$ taking into account the assigned content of *chloramphenicol CRS*.

STORAGE

Protected from light. If the substance is sterile, the container is also sterile, airtight and tamper-evident.

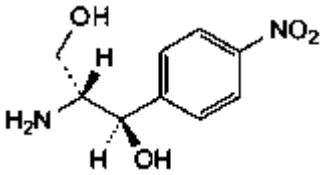
IMPURITIES

www.webofpharma.com

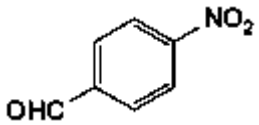
https://thuvienthuocngocanh.com/

Specified impurities A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. (1*R*,2*R*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol,



B. 4-nitrobenzaldehyde.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloramphenicol Capsules

General Notices

Action and use

Antibacterial.

DEFINITION

Chloramphenicol Capsules contain Chloramphenicol.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Suspend a quantity of the contents of the capsules containing 0.1 g of Chloramphenicol in 60 mL of *water* and extract with two 20-mL quantities of *petroleum spirit (boiling range, 120° to 160°)*. Wash the combined extracts with two 15-mL quantities of *water*, add the washings to the aqueous layer, extract with four 50-mL quantities of *ether* and evaporate the combined ether extracts. The residue complies with the following tests.

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethanol (96%)*.

(1) 1% w/v of the residue.

(2) 1% w/v of *chloramphenicol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *water*, 10 volumes of *methanol* and 90 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. Dissolve 10 mg of the residue in 2 mL of *ethanol (50%)*, add 4.5 mL of 1M *sulfuric acid* and 50 mg of *zinc powder* and allow to stand for 10 minutes. Decant the supernatant liquid or filter if necessary. Cool the resulting solution in ice and add 0.5 mL of *sodium nitrite solution* and, after 2 minutes, 1 g of *urea* followed by 1 mL of *2-naphthol solution* and 2 mL of 10M *sodium hydroxide*; a red colour is produced. Repeat the test omitting the zinc powder; no red colour is produced.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with *0.1M hydrochloric acid* if necessary, at the maximum at 278 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$, in the medium taking 297 as the value of A(1%, 1 cm) at the maximum at 278 nm.

2-Amino-1-(4-nitrophenyl)propane-1,3-diol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 40 mg of Chloramphenicol with 100 mL of the mobile phase for 10 minutes, add sufficient mobile phase to produce 200 mL, mix and filter.
(2) 0.0002% w/v of *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.
(3) 0.005% w/v of each of *chloramphenicol BPCRS* and *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to chloramphenicol and 2-amino-1-(4-nitrophenyl)propane-1,3-diol is at least 8.0.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to 2-amino-1-(4-nitrophenyl)-propane-1,3-diol is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of 20 capsules containing 0.2 g of Chloramphenicol in 800 mL of *water*, warming if necessary to effect solution, and add sufficient *water* to produce 1000 mL. Dilute 25 mL of this solution to 50 mL with the mobile phase.

(2) Dilute 1 volume of a 0.1% w/v solution of *chloramphenicol BPCRS* in *water* to 10 volumes with the mobile phase.

(3) 0.005% w/v of each of *chloramphenicol BPCRS* and *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 15 volumes of *acetonitrile* and 85 volumes of a 0.21% w/v solution of *sodium pentanesulfonate*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to chloramphenicol and 2-amino-1-(4-nitrophenyl)propane-1,3-diol is at least 8.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$ in the capsules using the declared content of $C_{11}H_{12}Cl_2N_2O_5$ in *chloramphenicol BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloramphenicol Ear Drops

General Notices

Action and use

Antibacterial.

DEFINITION

Chloramphenicol Ear Drops are a solution of Chloramphenicol in a suitable vehicle.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethanol (96%)*.

(1) Dilute a volume of the ear drops containing 0.1 g of Chloramphenicol to 10 mL.

(2) 1% w/v of *chloramphenicol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *water*, 10 volumes of *methanol* and 90 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Dilute a volume of the ear drops containing 50 mg of Chloramphenicol to 10 mL with *ethanol (50%)*. To 2 mL add 4.5 mL of 1M *sulfuric acid* and 50 mg of *zinc powder* and allow to stand for 10 minutes. Decant the supernatant liquid or filter if necessary. Cool the resulting solution in ice and add 0.5 mL of *sodium nitrite solution* and, after 2 minutes, 1 g of *urea* followed by 1 mL of *2-naphthol solution* and 2 mL of 10M *sodium hydroxide*; a red colour is produced. Repeat the test omitting the zinc powder; no red colour is produced.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

2-Amino-1-(4-nitrophenyl)propane-1,3-diol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the ear drops with sufficient of the mobile phase to produce a solution containing 0.050% w/v of Chloramphenicol.

(2) 0.0025% w/v of *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

(3) 0.005% w/v of each of *chloramphenicol BPCRS* and *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to chloramphenicol and 2-amino-1-(4-nitrophenyl)propane-1,3-diol is at least 8.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-amino-1-(4-nitrophenyl)-propane-1,3-diol is not greater than the area of the peak in the chromatogram obtained with solution (2) (5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the ear drops containing 25 mg of Chloramphenicol to 50 mL with water, mix and dilute 1 volume of the resulting solution to 5 volumes with the mobile phase.

(2) Dilute 1 volume of a 0.1% w/v solution of *chloramphenicol BPCRS* in *water* to 10 volumes with the mobile phase.

(3) 0.005% w/v of each of *chloramphenicol BPCRS* and *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 15 volumes of *acetonitrile* and 85 volumes of a 0.21% w/v solution of *sodium pentanesulfonate*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to chloramphenicol and 2-amino-1-(4-nitrophenyl)propane-1,3-diol is at least 8.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$ in the ear drops using the declared content of $C_{11}H_{12}Cl_2N_2O_5$ in *chloramphenicol BPCRS*.

STORAGE

Chloramphenicol Ear Drops should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloramphenicol Eye Drops

General Notices

Action and use

Antibacterial.

DEFINITION

Chloramphenicol Eye Drops are a sterile solution of Chloramphenicol in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

To a volume of the eye drops containing 50 mg of Chloramphenicol add 15 mL of *water* and extract with four 25-mL quantities of *ether*. Combine the extracts and evaporate to dryness. The dried residue complies with the following tests.

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethanol (96%)*.

(1) 1% w/v of the residue.

(2) 1% w/v of *chloramphenicol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *water*, 10 volumes of *methanol* and 90 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Dissolve 10 mg of the residue in 2 mL of *ethanol (50%)*, add 4.5 mL of 1M *sulfuric acid* and 50 mg of *zinc powder* and allow to stand for 10 minutes. Decant the supernatant liquid or filter if necessary. Cool the resulting solution in ice and add 0.5 mL of *sodium nitrite solution*

www.webofpharma.com

https://thuocngocanh.com/

and, after 2 minutes, 1 g of *urea* followed by 1 mL of *2-naphthol solution* and 2 mL of 10M *sodium hydroxide*; a red colour is produced.

Repeat the test omitting the zinc powder; no red colour is produced.

TESTS

Acidity or alkalinity

pH, 7.0 to 7.5, Appendix V L.

2-Amino-1-(4-nitrophenyl)propane-1,3-diol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the eye drops with sufficient of the mobile phase to produce a solution containing 0.05% w/v of Chloramphenicol.

(2) 0.004% w/v of *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

(3) 0.005% w/v of each of *chloramphenicol BPCRS* and *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to chloramphenicol and 2-amino-1-(4-nitrophenyl)propane-1,3-diol is at least 8.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-amino-1-(4-nitrophenyl)-propane-1,3-diol is not greater than the area of the peak in the chromatogram obtained with solution (2) (8%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the eye drops containing 5 mg of Chloramphenicol to 50 mL with the mobile phase.

(2) Dilute 1 volume of a 0.1% w/v solution of *chloramphenicol BPCRS* in *water* to 10 volumes with the mobile phase.

(3) 0.005% w/v of each of *chloramphenicol BPCRS* and *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 10 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 15 volumes of *acetonitrile* and 85 volumes of a 0.21% w/v solution of *sodium pentanesulfonate*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to chloramphenicol and 2-amino-1-(4-nitrophenyl)propane-1,3-diol is at least 8.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$ in the eye drops using the declared content of $C_{11}H_{12}Cl_2N_2O_5$ in *chloramphenicol BPCRS*.

STORAGE

Chloramphenicol Eye Drops should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloramphenicol Eye Ointment

General Notices

Action and use

Antibacterial.

DEFINITION

Chloramphenicol Eye Ointment is a sterile preparation containing Chloramphenicol in a suitable basis.

The eye ointment complies with the requirements stated under Eye Preparations and with the following requirements.

Content of chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the eye ointment containing 30 mg of Chloramphenicol with 10 mL of *petroleum spirit (boiling range, 40° to 60°)*, centrifuge and discard the supernatant liquid. Repeat this procedure using three 10-mL quantities of the same solvent. The dried residue complies with the following tests.

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethanol (96%)*.

(1) 1% w/v of the residue.

(2) 1% w/v of *chloramphenicol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *water*, 10 volumes of *methanol* and 90 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. Dissolve 10 mg of the residue in 2 mL of *ethanol (50%)*, add 4.5 mL of 1M *sulfuric acid* and 50 mg of *zinc powder* and allow to stand for 10 minutes. Decant the supernatant liquid or filter if necessary. Cool the resulting solution in ice and add 0.5 mL of *sodium nitrite solution* and, after 2 minutes, 1 g of *urea* followed by 1 mL of *2-naphthol solution* and 2 mL of 10M *sodium hydroxide*; a red colour is produced. Repeat the test omitting the zinc powder; no red colour is produced.

TESTS

2-Amino-1-(4-nitrophenyl)propane-1,3-diol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Suspend a quantity of the eye ointment containing 40 mg of Chloramphenicol in 50 mL of *petroleum spirit (boiling range, 40° to 60°)* and extract with successive quantities of 25, 25, 15 and 15 mL of a warm 0.21% w/v solution of *sodium pentanesulfonate*. Combine the extracts, add 15 mL of *acetonitrile* and 1 mL of *glacial acetic acid*, mix and dilute to 100 mL with a 0.21% w/v solution of *sodium pentanesulfonate*. Filter the resulting cooled solution through a 0.7-µm glass filter and then through a 0.45-µm nylon filter.

(2) Dilute 1 volume of a 0.04% w/v solution of *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in *water* to 100 volumes with the mobile phase.

(3) 0.005% w/v of each of *chloramphenicol BPCRS* and *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to chloramphenicol and 2-amino-1-(4-nitrophenyl)propane-1,3-diol is at least 8.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-amino-1-(4-nitrophenyl)-propane-1,3-diol is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Suspend a quantity of the eye ointment containing 10 mg of Chloramphenicol in 50 mL of *petroleum spirit (boiling range, 40° to 60°)* and extract with successive quantities of 25, 25, 15 and 15 mL of a warm 0.21% w/v solution of *sodium pentanesulfonate*. Combine the extracts, add 15 mL of *acetonitrile* and 1 mL of *glacial acetic acid*, mix and dilute to 100 mL with a 0.21% w/v solution of *sodium pentanesulfonate*. Filter the resulting cooled solution through a 0.7-µm glass filter and then through a 0.45-µm nylon filter.

(2) Dilute 1 volume of a 0.1% w/v solution of *chloramphenicol BPCRS* in *water* to 10 volumes with the mobile phase.

(3) 0.005% w/v of each of *chloramphenicol BPCRS* and *2-amino-1-(4-nitrophenyl)propane-1,3-diol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 278 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 15 volumes of *acetonitrile* and 85 volumes of a 0.21% w/v solution of *sodium pentanesulfonate*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to chloramphenicol and 2-amino-1-(4-nitrophenyl)propane-1,3-diol is at least 8.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$ in the eye ointment using the declared content of $C_{11}H_{12}Cl_2N_2O_5$ in *chloramphenicol BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

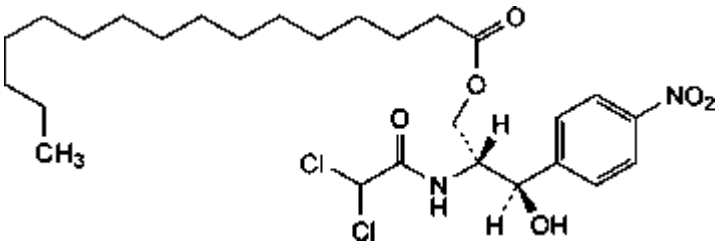
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloramphenicol Palmitate

General Notices

(Ph. Eur. monograph 0473)



$C_{27}H_{42}Cl_2N_2O_6$ 561.6 *530-43-8*

Action and use

Antibacterial.

Ph Eur

DEFINITION

Chloramphenicol palmitate contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of (2*R*,3*R*)-2-[(dichloroacetyl)amino]-3-hydroxy-3-(4-nitrophenyl)propyl hexadecanoate, calculated with reference to the dried substance.

Semi-synthetic product derived from a fermentation product.

CHARACTERS

A white or almost white, fine, unctuous powder, practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96 per cent), very slightly soluble in hexane.

It melts at 87 °C to 95 °C.

It shows polymorphism (5.9). The thermodynamically stable form has low bioavailability following oral administration.

IDENTIFICATION

A. Examine by thin-layer chromatography (2.2.27), using *TLC silanised silica gel plate R*.

Test solution Dissolve 50 mg of the substance to be examined in a mixture of 1 mL of *1 M sodium hydroxide* and 5 mL of *acetone R* and allow to stand for 30 min. Add 1.1 mL of *1 M hydrochloric acid* and 3 mL of *acetone R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 10 mg of *chloramphenicol CRS* in *acetone R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *palmitic acid R* in *acetone R* and dilute to 5 mL with the same solvent.

Reference solution (c) Dissolve 10 mg of the substance to be examined in *acetone R* and dilute to 5 mL with the same solvent.

Apply to the plate 4 µL of each solution. Develop over a path of 15 cm using a mixture of 30 volumes of a 100 g/L solution of *ammonium acetate R* and 70 volumes of *ethanol (96 per cent) R*. Allow the plate to dry in air and spray with a solution containing 0.2 g/L of *dichlorofluorescein R* and 0.1 g/L of *rhodamine B R* in *ethanol (96 per cent) R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. The chromatogram obtained with the test solution shows 3 spots corresponding in position to the principal spots in the chromatograms obtained with reference solutions (a), (b) and (c).

B. Dissolve 0.2 g in 2 mL of *pyridine R*, add 2 mL of a 100 g/L solution of *potassium hydroxide R* and heat on a water-bath. A red colour is produced.

C. Dissolve about 10 mg in 5 mL of *ethanol (96 per cent) R* and add 4.5 mL of *dilute sulfuric acid R* and 50 mg of *zinc powder R*. Allow to stand for 10 min and if necessary decant the supernatant or filter. Cool the solution in iced water and add 0.5 mL of *sodium nitrite solution R*. Allow to stand for 2 min and add 1 g of *urea R*, 2 mL of *strong sodium hydroxide solution R* and 1 mL of *β-naphthol solution R*. A red colour develops.

TESTS

Acidity

Dissolve 1.0 g in 5 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *ether R*, warming to 35 °C. Add 0.2 mL of *phenolphthalein solution R*. Not more than 0.4 mL of *0.1 M sodium hydroxide* is required to produce a pink colour persisting for 30 s.

Specific optical rotation (2.2.7)

Dissolve 1.25 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent. The specific optical rotation is + 22.5 to + 25.5.

Free chloramphenicol

Maximum 450 ppm. Dissolve 1.0 g, with gentle heating, in 80 mL of *xylene R*. Cool and shake with 3 quantities, each of 15 mL, of *water R*. Dilute the combined aqueous extracts to 50 mL with *water R* and shake with 10 mL of *toluene R*. Allow to separate and discard the toluene layer. Centrifuge a portion of the aqueous layer and measure the absorbance (*A*) (2.2.25) at the maximum at 278 nm using as the compensation liquid a blank solution having an absorbance not greater than 0.05.

Calculate the content of free chloramphenicol in parts per million from the expression:

$$\frac{A \times 10^4}{5.96}$$

Related substances

Examine by thin-layer chromatography (2.2.27), using *silica gel GF_{254} R* as the coating substance.

Test solution Dissolve 0.1 g of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Reference solution (a) Dissolve 20 mg of *chloramphenicol palmitate isomer CRS* in *acetone R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 10 mL with *acetone R*.

Reference solution (b) Dissolve 20 mg of *chloramphenicol dipalmitate CRS* in *acetone R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 10 mL with *acetone R*.

Reference solution (c) Dissolve 5 mg of *chloramphenicol CRS* in *acetone R* and dilute to 10 mL with the same solvent. Dilute 1 mL of this solution to 10 mL with *acetone R*.

Apply to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 10 volumes of *methanol R*, 40 volumes of *chloroform R* and 50 volumes of *cyclohexane R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. In the chromatogram obtained with the test solution, any spots due to chloramphenicol palmitate isomer and chloramphenicol dipalmitate are not more intense than the corresponding spots in the chromatograms obtained with reference solutions (a) and (b) respectively (2.0 per cent) and any spot, apart from the principal spot and the spots due to chloramphenicol palmitate isomer and chloramphenicol dipalmitate, is not more intense than the principal spot in the chromatogram obtained with reference solution (c) (0.5 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C at a pressure not exceeding 0.1 kPa for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

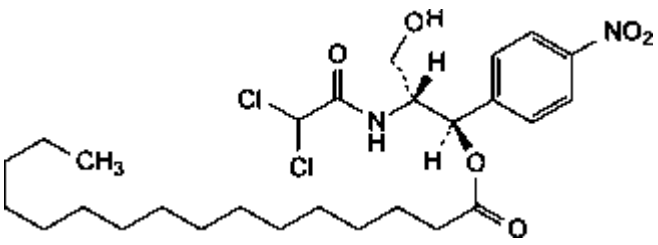
Dissolve 90.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 250.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) of the solution at the maximum at 271 nm.

Calculate the content of $C_{27}H_{42}Cl_2N_2O_6$ taking the specific absorbance to be 178.

STORAGE

Protected from light.

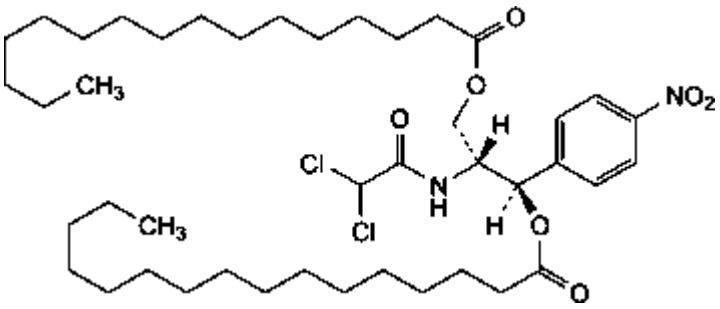
IMPURITIES



A. (1*R*,2*R*)-2-[(dichloroacetyl)amino]-3-hydroxy-1-(4-nitrophenyl)propyl hexadecanoate (chloramphenicol palmitate isomer),

www.webofpharma.com

https://thuocngocanh.com/



B. (1*R*,2*R*)-2-[(dichloroacetyl)amino]-1-(4-nitrophenyl)propane-1,3-diyl bishexadecanoate (chloramphenicol dipalmitate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

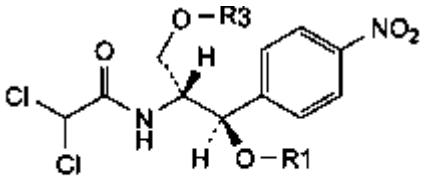
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloramphenicol Sodium Succinate

General Notices

(Ph. Eur. monograph 0709)



1 isomer : R1 = $CO\text{-}CH_2\text{-}CH_2\text{-}CO_2Na$, R3 = H

3 isomer : R1 = H, R3 = $CO\text{-}CH_2\text{-}CH_2\text{-}CO_2Na$

$C_{15}H_{15}Cl_2N_2NaO_8$ 445.2

Action and use

Antibacterial.

Preparation

Chloramphenicol Sodium Succinate Injection

Ph Eur

DEFINITION

Mixture in variable proportions of sodium (2*R*,3*R*)-2-[(dichloroacetyl)amino]-3-hydroxy-3-(4-nitrophenyl)propyl butanedioate (3 isomer) and of sodium (1*R*,2*R*)-2-[(dichloroacetyl)amino]-3-hydroxy-1-(4-nitrophenyl)propyl butanedioate (1 isomer).

Semi-synthetic product derived from a fermentation product.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white powder, hygroscopic.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 2 mL of *acetone R*.

Reference solution (a) Dissolve 20 mg of *chloramphenicol sodium succinate CRS* in 2 mL of *acetone R*.

Reference solution (b) Dissolve 20 mg of *chloramphenicol CRS* in 2 mL of *acetone R*.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *dilute acetic acid R*, *methanol R*, *chloroform R* (1:14:85 *V/V/V*).

Application 2 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The 2 principal spots in the chromatogram obtained with the test solution are similar in position and size to the 2 principal spots in the chromatogram obtained with reference solution (a); their positions are different from that of the principal spot in the chromatogram obtained with reference solution (b).

B. Dissolve about 10 mg in 1 mL of *ethanol (50 per cent V/V) R*, add 3 mL of a 10 g/L solution of *calcium chloride R* and 50 mg of *zinc powder R* and heat on a water-bath for 10 min. Filter the hot solution and allow to cool. Add 0.1 mL of *benzoyl chloride R* and shake for 1 min. Add 0.5 mL of *ferric chloride solution R1* and 2 mL of *chloroform R* and shake. The upper layer is light violet-red or purple.

C. Dissolve 50 mg in 1 mL of *pyridine R*. Add 0.5 mL of *dilute sodium hydroxide solution R* and 1.5 mL of *water R*. Heat in a water-bath for 3 min. A red colour develops. Add 2 mL of *nitric acid R* and cool under running water. Add 1 mL of *0.1 M silver nitrate*. A white precipitate is formed slowly.

D. It gives reaction (a) of sodium (2.3.1).

TESTS

pH (2.2.3)

6.4 to 7.0.

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 5.0 to + 8.0 (anhydrous substance).

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.50 g in *water R* and dilute to 10.0 mL with the same solvent.

Chloramphenicol and chloramphenicol disodium disuccinate

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 10.0 mg of *chloramphenicol CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase (solution A). Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 10.0 mg of *chloramphenicol disodium disuccinate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase (solution B). Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 25 mg of the substance to be examined in the mobile phase, add 5 mL of solution A and 5 mL of solution B and dilute to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 20 g/L solution of *phosphoric acid R*, *methanol R*, *water R* (5:40:55 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 20 µL.

System suitability Reference solution (c):

— the 2 peaks corresponding to those in the chromatograms obtained with reference solutions (a) and (b) are clearly separated from the peaks corresponding to the 2 principal peaks in the chromatogram obtained with the test solution; if necessary, adjust the methanol content of the mobile phase.

Limits:

— *chloramphenicol*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *chloramphenicol disodium disuccinate*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent).

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 0.500 g.

www.webofpharma.com

https://thuocngocanh.com/

Pyrogens (*2.6.8*)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of pyrogens, it complies with the test for pyrogens. Inject per kilogram of the rabbit's mass 2.5 mL of a solution in *water for injections R* containing 2 mg of the substance to be examined per millilitre.

ASSAY

Dissolve 0.200 g in *water R* and dilute to 500.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *water R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 276 nm.

Calculate the content of $C_{15}H_{15}Cl_2N_2NaO_8$, taking the specific absorbance to be 220.

STORAGE

In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloramphenicol Sodium Succinate Injection

General Notices

Action and use

Antibacterial.

DEFINITION

Chloramphenicol Sodium Succinate Injection is a sterile solution of Chloramphenicol Sodium Succinate in Water for Injections. It is prepared by dissolving Chloramphenicol Sodium Succinate for Injection in the requisite amount of Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Chloramphenicol Sodium Succinate Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

CHLORAMPHENICOL SODIUM SUCCINATE FOR INJECTION

DEFINITION

Chloramphenicol Sodium Succinate for Injection is a sterile material consisting of Chloramphenicol Sodium Succinate with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of chloramphenicol sodium succinate, calculated as $C_{11}H_{12}Cl_2N_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *acetone*.

(1) Dissolve a sufficient quantity of the contents of the sealed container to produce a solution containing the equivalent of 1% w/v of chloramphenicol.

(2) 1% w/v of *chloramphenicol sodium succinate EPCRS*.

(3) 1% w/v of *chloramphenicol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 2M *acetic acid*, 14 volumes of *methanol* and 85 volumes of *chloroform*.

CONFIRMATION

The two principal spots in the chromatogram obtained with solution (1) are similar in position and size to those in the chromatogram obtained with solution (2) and their positions are different from that of the principal spot in the chromatogram obtained with solution (3).

B. Dissolve 10 mg in 1 mL of *ethanol (50%)*, add 3 mL of a 1% w/v solution of *calcium chloride* and 50 mg of *zinc powder* and heat on a water bath for 10 minutes. Filter the hot solution, allow to cool, add 0.1 mL of *benzoyl chloride* and shake for 1 minute. Add 0.5 mL of *iron(III) chloride solution R1* and 2 mL of *chloroform* and shake. The aqueous layer is light violet-red to purple.

C. Yields reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 20.0% w/v of chloramphenicol, 6.0 to 7.0, Appendix V L.

Chloramphenicol and chloramphenicol disodium disuccinate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a sufficient quantity of the contents of the sealed container to give a solution containing the equivalent of 0.018% w/v of chloramphenicol.

(2) 0.00050% w/v of *chloramphenicol BPCRS*.

(3) 0.00050% w/v of *chloramphenicol disodium disuccinate EPCRS*.

(4) 0.00050% w/v of each of *chloramphenicol disodium disuccinate EPCRS* and *chloramphenicol BPCRS* and a sufficient quantity of the contents of the sealed container to give a solution containing the equivalent of 0.025% w/v of chloramphenicol.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (LiChrosorb RP-18, Hypersil ODS and Polygosil C18 5 µm are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

5 volumes of a 2% w/v solution of *orthophosphoric acid*, 40 volumes of *methanol* and 55 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless the two peaks in the chromatogram obtained with solution (4) corresponding to those in the chromatograms obtained with solutions (2) and (3) are clearly separated from the peaks corresponding to the two principal peaks in the chromatogram obtained with solution (1). If necessary, adjust the methanol content of the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the areas of any peaks corresponding to chloramphenicol and chloramphenicol disodium disuccinate are not greater than those of the principal peaks in the chromatograms obtained with solutions (2) and (3) respectively (2% of each).

Water

Not more than 5.0% w/w, Appendix IX C. Use 0.5 g.

Bacterial endotoxins

Carry out the test for *bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing 10 mg per mL (solution A). The endotoxin limit of solution A is 2.0 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Dissolve a quantity of the mixed contents of the 10 containers containing the equivalent of 0.2 g of chloramphenicol in *water* and add sufficient *water* to produce 500 mL. Dilute 5 mL of this solution to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 276 nm, Appendix II B. Calculate the content of chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$, in a container of average content weight taking 297 as the value of A(1%, 1 cm) at the maximum at 276 nm.

STORAGE

The sealed container should be protected from light.

LABELLING

The label of the sealed container states the quantity of Chloramphenicol Sodium Succinate contained in it in terms of the equivalent amount of chloramphenicol.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

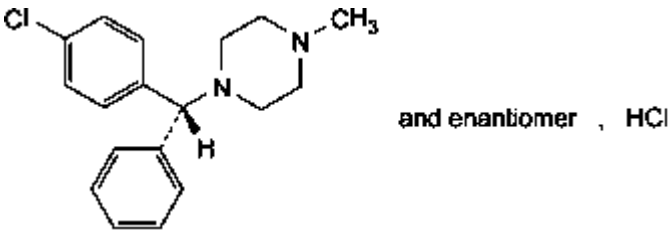
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Chlorcyclizine Hydrochloride

General Notices

(Ph. Eur. monograph 1086)



$C_{18}H_{22}Cl_2N_2$ 337.3 *14362-31-3*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

Chlorcyclizine hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (*RS*)-1-[(4-chlorophenyl)phenylmethyl]-4-methylpiperazine hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, freely soluble in water and in methylene chloride, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Dissolve 10.0 mg in a 5 g/L solution of *sulfuric acid R* and dilute to 100.0 mL with the same acid. Dilute 10.0 mL of the solution to 100.0 mL with a 5 g/L solution of *sulfuric acid R*. Examined between 215 nm and 300 nm (*2.2.25*), the solution shows an absorption maximum at 231 nm. The specific absorbance at the maximum is 475 to 525, calculated with reference to the dried substance.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *chlorcyclizine hydrochloride CRS*. Examine the substances prepared as discs.

www.webofpharma.com

https://thuocngocanh.com/

C. Examine the chromatograms obtained in the test for related substances (see Tests). The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

Dissolve 0.5 g in *water R* and dilute to 10 mL with the same solvent. The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. The pH of the solution is 5.0 to 6.0.

Related substances

Examine by thin-layer chromatography (2.2.27), using a plate coated with a suitable silica gel.

Test solution (a) Dissolve 0.20 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 5 mL of test solution (a) to 100 mL with *methanol R*.

Reference solution (a) Dissolve 10 mg of *chlorcyclizine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *methylpiperazine R* in *methanol R* and dilute to 50 mL with the same solvent.

Reference solution (c) Dilute 1 mL of test solution (b) to 25 mL with *methanol R*.

Reference solution (d) Dissolve 10 mg of *hydroxyzine hydrochloride CRS* and 10 mg of *chlorcyclizine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Apply separately to the plate 10 µL of each solution and develop over a path of 15 cm using a mixture of 2 volumes of *concentrated ammonia R*, 13 volumes of *methanol R* and 85 volumes of *methylene chloride R*. Allow the plate to dry in air and expose it to iodine vapour for 10 min. In the chromatogram obtained with test solution (a): any spot corresponding to methylpiperazine is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent); any spot, apart from the principal spot and any spot corresponding to methylpiperazine, is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.2 per cent). The test is not valid unless the chromatogram obtained with reference solution (d) shows two clearly separated spots.

Loss on drying (2.2.32)

Not more than 1.0 per cent, determined on 1.000 g by drying in an oven at 130 °C.

Sulfated ash (2.4.14)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuvienthuocngocanh.com/

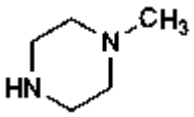
Dissolve 0.200 g in a mixture of 1 mL of *0.1 M hydrochloric acid* and 50 mL of *methanol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the two points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 33.73 mg of $C_{18}H_{22}Cl_2N_2$.

STORAGE

Store protected from light.

IMPURITIES



A. *N*-methylpiperazine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

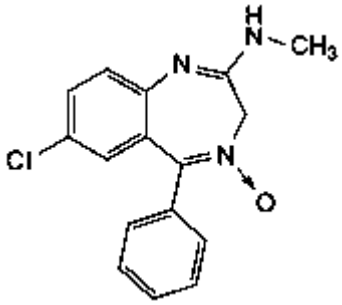
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlordiazepoxide

General Notices

(Ph. Eur. monograph 0656)



$C_{16}H_{14}ClN_3O$ 299.8 *58-25-3*

Action and use

Benzodiazepine.

Ph Eur

DEFINITION

7-Chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-amine 4-oxide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Almost white or light yellow, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *chlordiazepoxide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from bright light and prepare the solutions immediately before use*.

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *chlordiazepoxide impurity A CRS* in the mobile phase, add 25.0 mL of the test solution and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 4.0 mg of *aminochlorobenzophenone R* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *water R* (50:50 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 6 times the retention time of chlordiazepoxide.

Relative retention With reference to chlordiazepoxide (retention time = about 3.6 min): impurity A = about 0.7; impurity B = about 2.3; impurity C = about 3.9.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and chlordiazepoxide.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent),

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent),

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g, with heating if necessary, in 80 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (2.2.20).

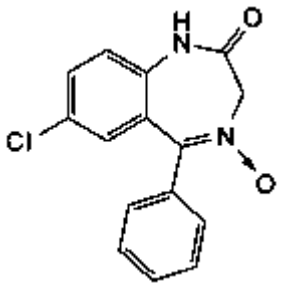
1 mL of *0.1 M perchloric acid* is equivalent to 29.98 mg of $C_{16}H_{14}ClN_3O$.

STORAGE

Protected from light.

IMPURITIES

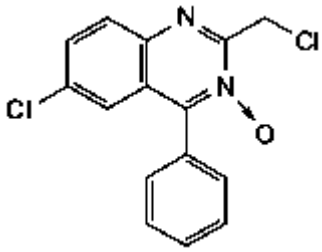
Specified impurities *A, B, C.*



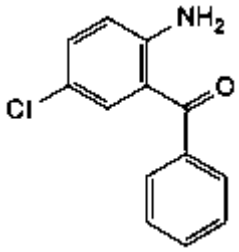
A. 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide,

www.webofpharma.com

https://thuocngocanh.com/



B. 6-chloro-2-(chloromethyl)-4-phenylquinazoline 3-oxide,



C. (2-amino-5-chlorophenyl)phenylmethanone (aminochlorobenzophenone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlordiazepoxide Capsules

General Notices

Action and use

Benzodiazepine.

DEFINITION

Chlordiazepoxide Capsules contain Chlordiazepoxide Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of chlordiazepoxide hydrochloride, $C_{16}H_{14}ClN_3O,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the following procedure protected from light. Shake a quantity of the mixed capsule contents containing 20 mg of Chlordiazepoxide Hydrochloride with 150 mL of *0.1M hydrochloric acid* for 20 minutes. Add sufficient 0.1 M *hydrochloric acid* to produce 200 mL and filter. Dilute 10 mL of the filtrate to 100 mL with *0.1M hydrochloric acid*. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 246 nm and 308 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a sample of the medium and measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 308 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of chlordiazepoxide hydrochloride, $C_{16}H_{14}ClN_3O,HCl$, in the medium taking 292 as the value of A(1%, 1 cm) at the maximum at 308 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use and protected from light.

(1) Shake a quantity of the mixed capsule contents containing 20 mg of Chlordiazepoxide Hydrochloride with 50 mL of the mobile phase, dilute to 100 mL with the mobile phase and filter.

(2) Dilute 3 volumes of solution (1) to 100 volumes with the mobile phase.

(3) Dilute 2 volumes of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of this solution to 10 volumes with the mobile phase.

(4) 0.00004% w/v of *aminochlorobenzophenone*(impurity C) in the mobile phase.

(5) 0.0002% w/v of *chlordiazepoxide impurity A EPCRS* and 0.0002% w/v of *chlordiazepoxide hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

(g) For solutions (1) and (4) allow the chromatography to proceed for 6 times the retention time of the peak due to chlordiazepoxide.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity A and chlordiazepoxide is at least 5.0.

When the chromatograms are recorded under the prescribed conditions the retention times relative to chlordiazepoxide (retention time about 3.6 min) are impurity A, about 0.7 and impurity C, about 3.9.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (3%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak due to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the impurities is not greater than 3.4%.

Disregard any peak with an area less than half the area of the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use and protected from light.

(1) Shake a quantity of the mixed contents of 20 capsules containing 20 mg of Chlordiazepoxide Hydrochloride with 50 mL of the mobile phase, dilute to 100 mL with the mobile phase and filter. Dilute 10 mL of this solution to 100 mL with the mobile phase.
(2) 0.002% w/v of *chlordiazepoxide hydrochloride BPCRS* in the mobile phase.
(3) 0.0002% w/v of *chlordiazepoxide impurity A EPCRS* and 0.0002% w/v *chlordiazepoxide hydrochloride BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and chlordiazepoxide is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{14}ClN_3O$,HCl in the capsules using the declared content of $C_{16}H_{14}ClN_3O$,HCl in *chlordiazepoxide hydrochloride BPCRS*.

STORAGE

Chlordiazepoxide Capsules should be protected from light.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

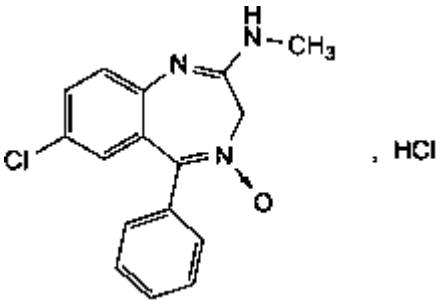
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlordiazepoxide Hydrochloride

General Notices

(Ph. Eur. monograph 0474)



$C_{16}H_{15}Cl_2N_3O$ 336.2 *438-41-5*

Action and use

Benzodiazepine.

Preparations

Chlordiazepoxide Capsules

Chlordiazepoxide Tablets

Ph Eur

DEFINITION

7-Chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-amine 4-oxide hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellow, crystalline powder.

Solubility

Soluble in water, sparingly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison chlordiazepoxide hydrochloride CRS.

If the spectra obtained in the solid state show differences, dissolve 100 mg in 9 mL of water R and add 1 mL of dilute sodium hydroxide solution R. Extract with 10 mL of methylene chloride R in a separating funnel. Evaporate the organic layer and dry the residue obtained at 100-105 °C. Proceed in the same way with the reference substance. Record new spectra using the residues.

B. Dissolve 50 mg in 5 mL of water R, add 1 mL of dilute ammonia R1, mix, allow to stand for 5 min and filter. Acidify the filtrate with dilute nitric acid R. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution GY_6 (2.2.2, Method II).

Dissolve 2.5 g in water R and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the following operations protected from bright light and prepare the solutions immediately before use.*

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of chlordiazepoxide impurity A CRS in the mobile phase, add 25.0 mL of the test solution and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 4.0 mg of aminochlorobenzophenone R in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase acetonitrile R, water R (50:50 *V/V*).

Flow rate 1.0 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 6 times the retention time of chlordiazepoxide.

Relative retention With reference to chlordiazepoxide (retention time = about 3.6 min): impurity A = about 0.7; impurity B = about 2.3; impurity C = about 3.9.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and chlordiazepoxide.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent),

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent),

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 33.62 mg of $C_{16}H_{15}Cl_2N_3O$.

STORAGE

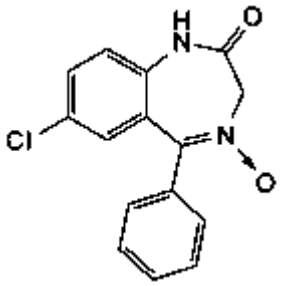
Protected from light.

IMPURITIES

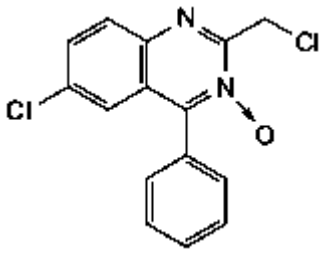
Specified impurities *A, B, C.*

www.webofpharma.com

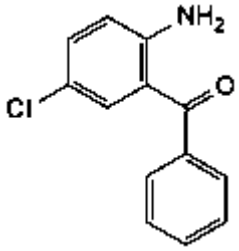
https://thuocngocanh.com/



A. 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide,



B. 6-chloro-2-(chloromethyl)-4-phenylquinazoline 3-oxide,



C. (2-amino-5-chlorophenyl)phenylmethanone (aminochlorobenzophenone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlordiazepoxide Tablets

General Notices

Chlordiazepoxide Hydrochloride Tablets

Action and use

Benzodiazepine.

DEFINITION

Chlordiazepoxide Tablets contain Chlordiazepoxide Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of chlordiazepoxide, $C_{16}H_{14}ClN_3O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake 10 whole tablets with 150 mL of *0.1M hydrochloric acid* for 20 minutes, add sufficient *0.1M hydrochloric acid* to produce 250 mL and filter. Dilute 10 mL of the filtrate with sufficient *0.1M hydrochloric acid* to produce a solution containing the equivalent of 0.0010% w/v of chlordiazepoxide. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 246 nm and 308 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 308 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://nhathuocngocanh.com/

Calculate the total content of chlordiazepoxide, $C_{16}H_{14}ClN_3O$, in the medium taking 327 as the value of A(1%, 1 cm) at the maximum at 308 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use and protected from light.

(1) Shake a quantity of powdered tablets containing the equivalent of 20 mg of chlordiazepoxide with 50 mL of the mobile phase, dilute to 100 mL with the mobile phase and filter.
(2) Dilute 3 volume of solution (1) to 100 volumes with the mobile phase.
(3) Dilute 2 volumes of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of this solution to 10 volumes with the mobile phase.
(4) 0.00004% w/v of *aminochlorobenzophenone* in the mobile phase.
(5) 0.0002% w/v of *chlordiazepoxide impurity A EPCRS* and 0.0002% w/v of *chlordiazepoxide hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 10 µL of each solution.
(g) For solutions (1) and (4) allow the chromatography to proceed for 6 times the retention time of the peak due to chlordiazepoxide.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to impurity A and chlordiazepoxide is at least 5.0.

When the chromatograms are recorded under the prescribed conditions the retention times relative to chlordiazepoxide (retention time about 3.6 min) are impurity A, about 0.7 and aminochlorobenzophenone, about 3.9.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak due to aminochlorobenzophenone is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of all impurities is not greater than 3.4%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use and protected from light.

(1) Weigh and powder 20 tablets. Shake a quantity of powdered tablets containing the equivalent of 20 mg of chlordiazepoxide with 50 mL of the mobile phase, dilute to 100 mL with the mobile phase and filter. Dilute 10 mL of this solution to 100 mL with the mobile phase.

(2) 0.002% w/v of *chlordiazepoxide hydrochloride BPCRS* in the mobile phase.

(3) 0.0002% w/v of *chlordiazepoxide impurity A EPCRS* and 0.0002% w/v of *chlordiazepoxide hydrochloride BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and chlordiazepoxide is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{14}ClN_3O$ in the tablets using the declared content of $C_{16}H_{14}ClN_3O$,HCl in *chlordiazepoxide hydrochloride BPCRS*. Each mg of $C_{16}H_{14}ClN_3O$,HCl is equivalent to 0.8916 mg of $C_{16}H_{14}ClN_3O$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of chlordiazepoxide.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

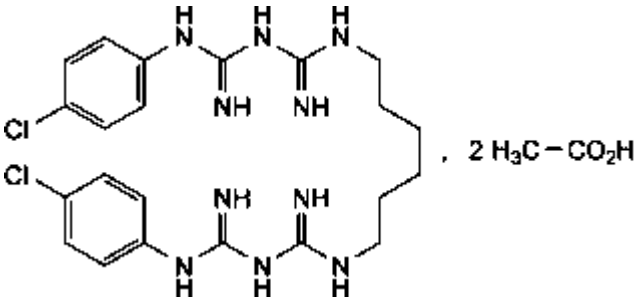
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorhexidine Acetate

General Notices

(Chlorhexidine Diacetate, Ph. Eur. monograph 0657)



$C_{26}H_{38}Cl_2N_{10}O_4$ 626 *56-95-1*

Action and use

Antiseptic.

Preparation

Chlorhexidine Irrigation Solution

Ph Eur

DEFINITION

N^1,$N^{1\prime}$-(Hexane-1,6-diyl)bis[N^3-(4-chlorophenyl)imidodicarbonimidic diamide] diacetate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, microcrystalline powder.

Solubility

Sparingly soluble in water, soluble in ethanol (96 per cent), slightly soluble in glycerol and in propylene glycol.

IDENTIFICATION

https://thuocngocanh.com/

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *chlorhexidine diacetate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 5 mg of *chlorhexidine diacetate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *water R*, *ethanol (96 per cent) R*, *methylene chloride R* (7:10:40:50 *V/V/V/V*).

Application 5 µL; the volume may be adapted based on the type of plate used.

Development Over 2/3 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

Detection B Treat with *copper sulfate solution R* and examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of acetates (2.3.1).

TESTS

Impurity P (chloroaniline)

Maximum 500 ppm.

Test solution Dissolve 0.20 g in 25 mL of *water R* with shaking if necessary. Add 1 mL of *hydrochloric acid R* and dilute to 30 mL with *water R*. Add rapidly and with thorough mixing after each addition: 5 mL of a 103 g/L solution of *hydrochloric acid R*, 0.35 mL of *sodium nitrite solution R*, 2 mL of a 50 g/L solution of *ammonium sulfamate R*, 5 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* and 1 mL of *ethanol (96 per cent) R*; transfer quantitatively to a volumetric flask, dilute to 50.0 mL with *water R* and allow to stand for 30 min.

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions Prepare reference solutions representing respectively 50 ppm, 100 ppm, 200 ppm, 500 ppm and 600 ppm of *chloroaniline R* (impurity P) in the test sample as follows: dilute 1.0 mL, 2.0 mL, 4.0 mL, 10.0 mL and 12.0 mL of a solution containing 0.010 g/L of *chloroaniline R* (impurity P) in *dilute hydrochloric acid R* to 20 mL with *water R*. Then, add 10 mL of *water R*. Add rapidly and with thorough mixing after each addition: 5 mL of a 103 g/L solution of *hydrochloric acid R*, 0.35 mL of *sodium nitrite solution R*, 2 mL of a 50 g/L solution of *ammonium sulfamate R*, 5 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* and 1 mL of *ethanol (96 per cent) R*; transfer each solution quantitatively to a volumetric flask, dilute to 50.0 mL with *water R* and allow to stand for 30 min.

Measure the absorbance (*2.2.25*) of each reference solution at 556 nm and plot a calibration curve.

Measure the absorbance (*2.2.25*) of the test solution at 556 nm. Determine the concentration of chloroaniline from the calibration curve.

Related substances

Liquid chromatography (*2.2.29*). *Store the solutions at a temperature not exceeding 12 °C.*

Test solution Dissolve 0.140 g of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *chlorhexidine for system suitability CRS* (containing impurities A, B, H, I, K, N and O) in 1.0 mL of mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 20 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *acetonitrile R* and 80 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *water for chromatography R*;

— *mobile phase B*: mix 10 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *water for chromatography R* and 90 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 32	100 → 80	0 → 20
32 - 37	80	20
37 - 47	80 → 70	20 → 30

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
47 - 54	70	30

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *chlorhexidine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, H, I, K, N and O.

Relative retention With reference to chlorhexidine (retention time = about 35 min): impurity N = about 0.35; impurity B = about 0.36; impurity A = about 0.6; impurity H = 0.85; impurity O = about 0.90; impurity I = about 0.91; impurity K = about 1.4.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity N.

Limits:

— *sum of impurities I and O*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity K*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities A, H, N*: for each impurity, not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 3.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.15 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

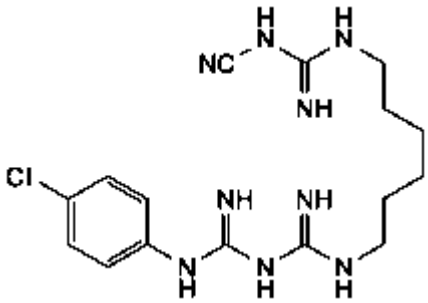
Dissolve 0.140 g in 100 mL of *anhydrous acetic acid R* and titrate with *0.1 M perchloric acid*. Determine the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 15.64 mg of $C_{26}H_{38}Cl_2N_{10}O_4$.

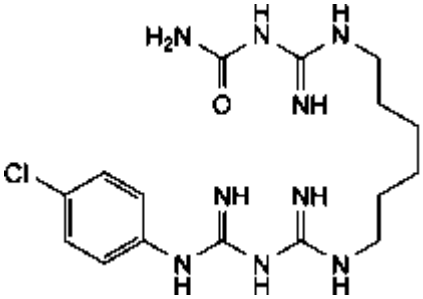
IMPURITIES

Specified impurities *A, H, I, K, N, O, P.*

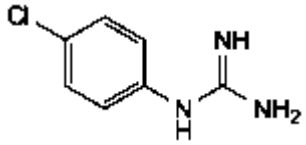
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, E, F, G, M.*



A. N^1-(4-chlorophenyl)-N^3-[6-[(*N*-cyanocarbamimidoyl)amino]hexyl]imidodicarbonimidic diamide,



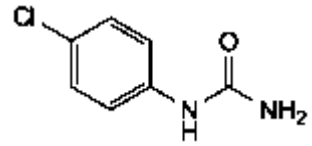
B. *N*-[*N*-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]carbamimidoyl]urea,



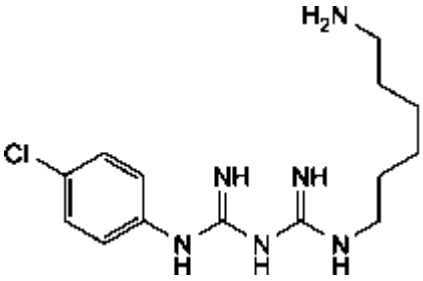
E. *N*-(4-chlorophenyl)guanidine,

www.webofpharma.com

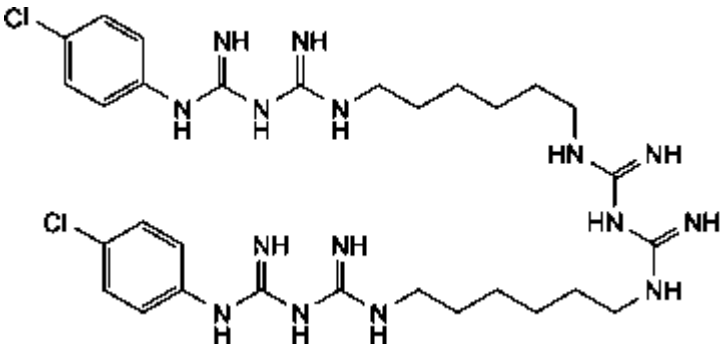
https://thuocngocanh.com/



F. *N*-(4-chlorophenyl)urea,

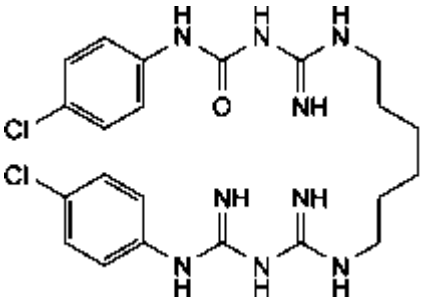


G. N^1-(6-aminohexyl)-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,

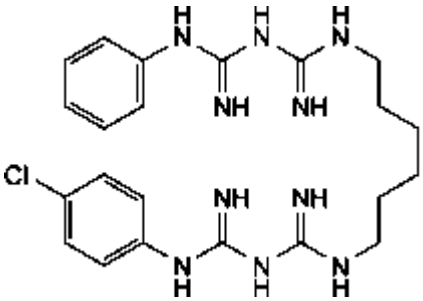


H. N^1,$N^{1\prime}$-[azanediylbis(carbonimidoylazanediylhexane-6,1-diyl)]bis[N^3-(4-chlorophenyl)imidodicarbonimidic diamide],

I. unknown structure,



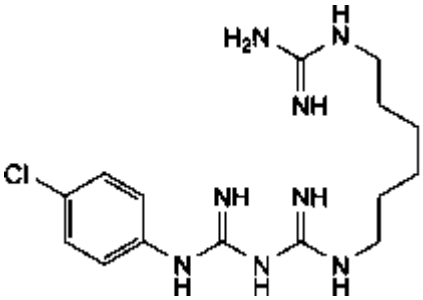
K. *N*-(4-chlorophenyl)-*N*′-[*N*-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]carbamimidoyl]urea,



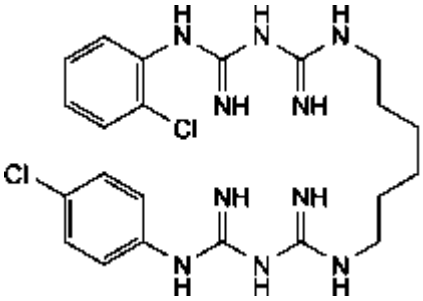
www.webofpharma.com

https://thuocngocanh.com/

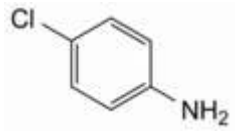
M. N^1-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]-N^3-phenylimidodicarbonimidic diamide,



N. N^1-[6-(carbamimidoylamino)hexyl]-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,



O. N^1-[6-[[*N*-[*N*-(2-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,



P. 4-chloroaniline.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorhexidine Gluconate Dental Gel

General Notices

Chlorhexidine Gluconate Gel

Action and use

Antiseptic.

DEFINITION

Chlorhexidine Gluconate Dental Gel is a solution of Chlorhexidine Gluconate in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of chlorhexidine gluconate, $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Disperse a quantity of the gel containing 5 mg of Chlorhexidine Gluconate in 10 mL of *water*, mix and dilute to 500 mL with *water*. The *light absorption* of the resulting solution, Appendix II B, in the range 200 to 320 nm exhibits two maxima, at 231 nm and 255 nm, and two minima, at 222 nm and 242 nm.

B. Place a quantity of the gel on a white tile and add a drop of *bromine water*. A reddish-yellow colour is produced.

C. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to chlorhexidine in the chromatogram obtained with solution (1).

TESTS

Acidity

pH, 5.0 to 7.0, Appendix V L.

4-Chloroaniline

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

Dissolve 80 mg of *2,6-dimethylaniline* (internal standard) in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 100 mL and dilute 1 volume of this solution to 100 volumes with 0.01M *hydrochloric acid* (solvent A).

(1) Shake a quantity of the gel containing 0.5 g of Chlorhexidine Gluconate with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution*, allow to separate and discard the lower layer. Shake the upper

www.webofpharma.com

https://thuocngocanh.com/

layer with *anhydrous sodium sulfate* and filter through silica-treated filter paper (Whatman 1PS is suitable), add 100 µL of *heptafluorobutyric anhydride* and shake for 30 seconds. Allow the solution to stand for 2 minutes, add 5 mL of 0.6M *sodium hydrogen carbonate solution*, shake, allow to separate and use the upper layer.

(2) Add 2 mL of solvent A to a quantity of the gel containing 0.5 g of Chlorhexidine Gluconate, shake with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution*, allow to separate and discard the lower layer. Shake the upper layer with *anhydrous sodium sulfate* and filter through silica treated filter paper (Whatman 1PS is suitable), add 100 µL of *heptafluorobutyric anhydride* and shake for 30 seconds. Allow the solution to stand for 2 minutes, add 5 mL of 0.6M *sodium hydrogen carbonate solution*, shake, allow to separate and use the upper layer.

REFERENCE SOLUTIONS

Prepare a series of reference solutions in the following manner. Dissolve 25 mg of *4-chloroaniline* in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 200 mL and dilute 1 volume to 10 volumes with the same solvent. To separate 0, 2, 4, 6 and 8 mL volumes of this solution (containing 0, 25, 50, 75 and 100 µg of 4-chloroaniline) add 2 mL of solvent A and sufficient *water* to produce 50 mL, shake with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane*, and 5 mL of 0.6M *sodium hydrogen carbonate solution* allow to separate and discard the lower layer. Shake the upper layer with *anhydrous sodium sulfate* and filter through silica-treated filter paper (Whatman 1PS is suitable), add 100 µL of *heptafluorobutyric anhydride* and shake for 30 seconds. Allow the solution to stand for 2 minutes, add 5 mL of 0.6M *sodium hydrogen carbonate solution*, shake, allow to separate and use the upper layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *silanised diatomaceous support* (100 to 120 mesh) coated with 15% w/w of cyanopropylmethylphenyl methyl silicone fluid (OV-225 is suitable).
(b) Use a flow rate of 50 mL per minute.
(c) Use a column temperature of 190°.
(d) Use an inlet port temperature of 200°.
(e) Use a detector temperature of 270°.
(f) Use *nitrogen* as the carrier gas.
(g) Use an electron capture detector.
(h) Inject 1 µL of each solution.

Inject the reference solutions and construct a calibration curve of the concentration of 4-chloroaniline against the ratio of the area of the peak corresponding to 4-chloroaniline to the area of the peak due to the internal standard.

LIMITS

In the chromatogram obtained with solution (2) determine the ratio of the area of any peak due to 4-chloroaniline to the area of the peak due to the internal standard and hence calculate the content of 4-chloroaniline in the gel. Not more than 20 ppm.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of a 0.080% w/v solution of *diphenylamine* (internal standard) in the mobile phase to 5 mL of a 0.070% w/v solution of *chlorhexidine acetate BPCRS* in the mobile phase and dilute to 100 mL with the mobile phase.
(2) Mix a quantity of the gel containing 5 mg of Chlorhexidine Gluconate with sufficient of the mobile phase to produce 100 mL.

www.webofpharma.com

https://thuocngocanh.com/

(3) Prepare in the same manner as solution (2) but add 5 mL of the internal standard solution before diluting to 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

0.01M *sodium octanesulfonate* in *methanol (73%)* adjusted to pH 3.0 with *glacial acetic acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$ in the gel from the declared content of $C_{22}H_{30}Cl_2N_{10}$ in *chlorhexidine acetate BPCRS*.

Each mg of $C_{22}H_{30}Cl_2N_{10}$ is equivalent to 1.776 mg of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorhexidine Gluconate Eye Drops

General Notices

Chlorhexidine Digluconate Eye Drops

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Antiseptic.

DEFINITION

Chlorhexidine Gluconate Eye Drops are a sterile solution of Chlorhexidine Gluconate in Purified Water. They are usually prepared from Chlorhexidine Gluconate Solution.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of chlorhexidine gluconate, $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$

95.0 to 115.0% of the stated amount.

IDENTIFICATION

A. Add 10 mL of *concentrated ammonia*, drop wise, to a volume of the eye drops containing the equivalent of 20 mg of chlorhexidine gluconate which has previously been cooled in ice. Centrifuge at 3000 rpm for 10 minutes, discard the supernatant liquid and transfer the residue to a filter which has previously been treated with *water* (Whatman GF/F paper is suitable); allow to stand until the ammonia has evaporated. Wash the residue with 10 mL of *water* and dissolve in *ethanol (70%)*. Evaporate the solvent under a stream of *nitrogen* and dry the residue at 105° for one hour. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of chlorhexidine *(RS 449)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the peak due to chlorhexidine in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 5.0 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dilute a volume of the eye drops, if necessary, to produce a solution containing the equivalent of 0.02% w/v of chlorhexidine gluconate.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 10 volumes.

(4) 0.001% w/v of *4-chloroaniline*.

(5) Dilute 1 volume of solution (4) and 2 volumes of a 0.0035% w/v solution of *chlorhexidine acetate BPCRS* to 20 volumes.

When the chromatograms are recorded under the prescribed conditions the retention time of chlorhexidine is about 13 minutes and the relative retention of 4-chloroaniline is about 0.3.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18(2) is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 6 times the retention time of chlorhexidine.

Equilibrate the column with mobile phase for at least 1 hour.

MOBILE PHASE

120 volumes of *glacial acetic acid*, 270 volumes of *water* and 730 volumes of *methanol* containing 0.2% w/v of *sodium octanesulfonate*.

SYSTEM SUITABILITY

Use the chromatogram obtained with solution (4) to identify the peak due to 4-chloroaniline.

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the two principal peaks is at least 23.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to 4-chloroaniline is not greater that the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of not more than one *secondary peak* is greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all the *secondary peaks* is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the eye drops, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.02% w/v of chlorhexidine gluconate.

(2) 0.014% w/v of *chlorhexidine acetate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Partisil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *perchloric acid*, 35 volumes of *methanol* and 64 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$ in the eye drops using the declared content of $C_{22}H_{30}Cl_2N_{10}$ in *chlorhexidine acetate BPCRS*. Each mg of $C_{22}H_{30}Cl_2N_{10}$ is equivalent to 1.776 mg of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$.

STORAGE

Chlorhexidine Gluconate Eye Drops should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of chlorhexidine gluconate.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuathuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

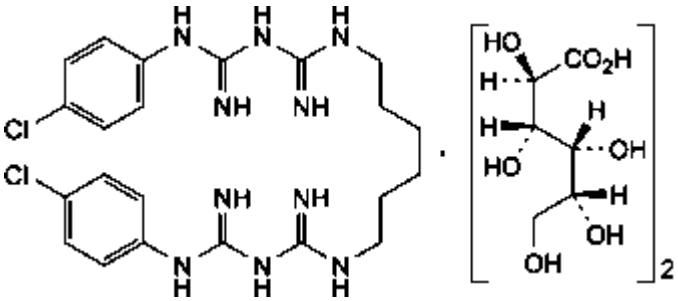
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorhexidine Gluconate Solution

General Notices

(Chlorhexidine Digluconate Solution, Ph. Eur. monograph 0658)



$C_{34}H_{54}Cl_2N_{10}O_{14}$ 898 *18472-51-0*

Action and use

Antiseptic.

Preparations

Chlorhexidine Gluconate Eye Drops

Chlorhexidine Gluconate Dental Gel

Chlorhexidine Irrigation Solution

Chlorhexidine Gluconate Umbilical Cord Gel

Chlorhexidine Mouthwash

Lidocaine and Chlorhexidine Gel

Ph Eur

DEFINITION

N^1,$N^{1\prime}$-(Hexane-1,6-diyl)bis[N^3-(4-chlorophenyl)imidodicarbonimidic diamide] di-D-gluconate.

Content

190 g/L to 210 g/L.

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

Appearance

Almost colourless or pale-yellowish liquid.

Solubility

Miscible with water, with not more than 3 parts of acetone and with not more than 5 parts of ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation To 1 mL add 40 mL of water R, cool in iced water, make alkaline to titan yellow paper R by adding dropwise, and with stirring, strong sodium hydroxide solution R and add 1 mL in excess. Filter, wash the precipitate with water R until the washings are free from alkali and recrystallise from ethanol (70 per cent V/V) R. Dry at 100-105 °C. Examine the residue.

Comparison chlorhexidine CRS.

B. Thin-layer chromatography (2.2.27).

Test solution Dilute 10.0 mL of the preparation to be examined to 50 mL with water R.

Reference solution Dissolve 25 mg of calcium gluconate CRS in 1 mL of water R.

Plate TLC silica gel plate R.

Mobile phase concentrated ammonia R, ethyl acetate R, water R, ethanol (96 per cent) R (10:10:30:50 *V/V/V/V*).

Application 5 µL.

Development Over 1/2 of the plate.

Drying At 100 °C for 20 min and allow to cool.

Detection Spray with a solution containing 25 g/L of ammonium molybdate R and 10 g/L of cerium sulfate R in dilute sulfuric acid R, and heat at 110 °C for about 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 1 mL add 40 mL of water R, cool in iced water, make alkaline to titan yellow paper R by adding dropwise, and with stirring, strong sodium hydroxide solution R and add 1 mL in excess. Filter, wash the precipitate with water R until the washings are free from alkali and recrystallise from ethanol (70 per cent V/V) R. Dry at 100-105 °C. The residue melts (2.2.14) at 132 °C to 136 °C.

D. To 0.05 mL add 5 mL of a 10 g/L solution of cetrimide R, 1 mL of strong sodium hydroxide solution R and 1 mL of bromine water R; a deep red colour is produced.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Relative density (2.2.5)

1.06 to 1.07.

pH (2.2.3)

5.5 to 7.0.

Dilute 5.0 mL to 100 mL with *carbon dioxide-free water R*.

Impurity P (chloroaniline)

Maximum 500 ppm, calculated with reference to chlorhexidine digluconate solution.

Test solution Dilute 0.20 g of the preparation to be examined to 30 mL with *water R*. Add rapidly and with thorough mixing after each addition: 5 mL of a 103 g/L solution of *hydrochloric acid R*, 0.35 mL of *sodium nitrite solution R*, 2 mL of a 50 g/L solution of *ammonium sulfamate R*, 5 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* and 1 mL of *ethanol (96 per cent) R*; transfer quantitatively to a volumetric flask, dilute to 50.0 mL with *water R* and allow to stand for 30 min.

Reference solutions Prepare reference solutions representing respectively 50 ppm, 100 ppm, 200 ppm, 500 ppm and 600 ppm of *chloroaniline R* (impurity P) in the test sample as follows: dilute 1.0 mL, 2.0 mL, 4.0 mL, 10.0 mL and 12.0 mL of a solution containing 0.010 g/L of *chloroaniline R* (impurity P) in *dilute hydrochloric acid R* to 20 mL with *water R*. Then, add 10 mL of *water R*. Add rapidly and with thorough mixing after each addition: 5 mL of a 103 g/L solution of *hydrochloric acid R*, 0.35 mL of *sodium nitrite solution R*, 2 mL of a 50 g/L solution of *ammonium sulfamate R*, 5 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* and 1 mL of *ethanol (96 per cent) R*; transfer each solution quantitatively to a volumetric flask, dilute to 50.0 mL with *water R* and allow to stand for 30 min.

Measure the absorbance (2.2.25) of each reference solution at 556 nm and plot a calibration curve.

Measure the absorbance (2.2.25) of the test solution at 556 nm. Determine the concentration of chloroaniline from the calibration curve.

Related substances

Liquid chromatography (2.2.29). *Store the solutions at a temperature not exceeding 12 °C.*

Test solution Dilute 1.0 mL of the preparation to be examined to 100.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *chlorhexidine for system suitability CRS* (containing impurities A, B, F, G, H, I, J, K, L, N and O) in 1.0 mL of mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 20 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *acetonitrile R* and 80 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *water R*;

— *mobile phase B*: mix 10 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *water R* and 90 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 32	100 → 80	0 → 20
32 - 37	80	20
37 - 47	80 → 70	20 → 30
47 - 54	70	30

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *chlorhexidine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, F, G, H, I, J, K, L, N and O.

Relative retention With reference to chlorhexidine (retention time = about 35 min): impurity L = about 0.23; impurity Q = about 0.24; impurity G = about 0.25; impurity N = about 0.35; impurity B = about 0.36; impurity F = about 0.5; impurity A = about 0.6; impurity H = about 0.85; impurity O = about 0.90; impurity I = about 0.91; impurity J = about 0.96; impurity K = about 1.4.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurities L and G;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity N.

Limits:

— *impurity N*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity H*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *impurities A, J , K*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *sum of impurities I and O*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity G*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities B, F, L, Q*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

ASSAY

Determine the density (2.2.5) of the preparation to be examined. Transfer 1.00 g to a 250 mL beaker and add 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 22.44 mg of $C_{34}H_{54}Cl_2N_{10}O_{14}$.

STORAGE

Protected from light.

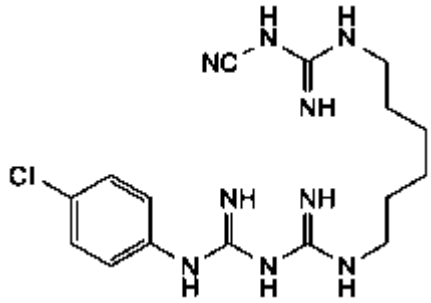
IMPURITIES

Specified impurities *A, B, F, G, H, I, J, K, L, N, O, P, Q.*

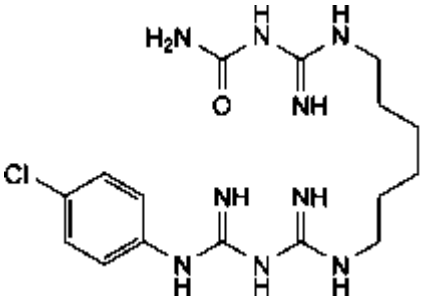
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, M.*

www.webofpharma.com

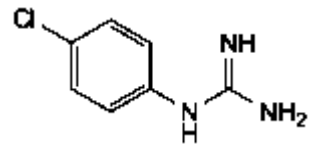
https://thuocngocanh.com/



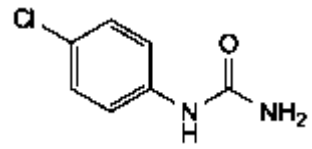
A. N^1-(4-chlorophenyl)-N^3-[6-[(*N*-cyanocarbamimidoyl)amino]hexyl]imidodicarbonimidic diamide,



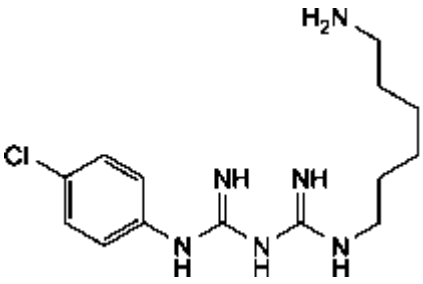
B. *N*-[*N*-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]carbamimidoyl]urea,



E. *N*-(4-chlorophenyl)guanidine,



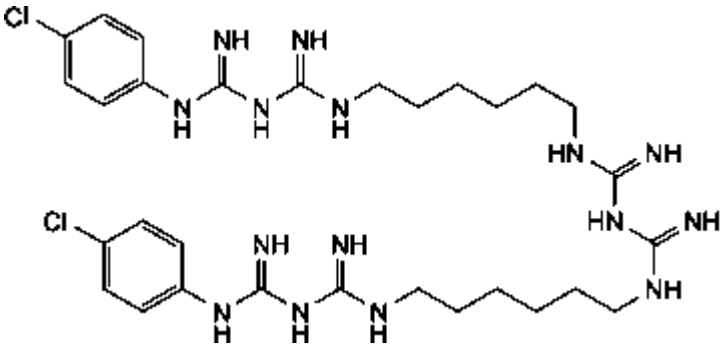
F. *N*-(4-chlorophenyl)urea,



G. N^1-(6-aminohexyl)-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,

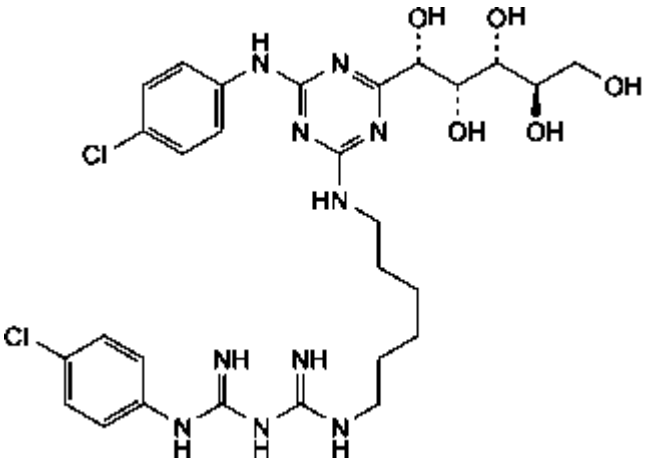
www.webofpharma.com

https://thuocngocanh.com/

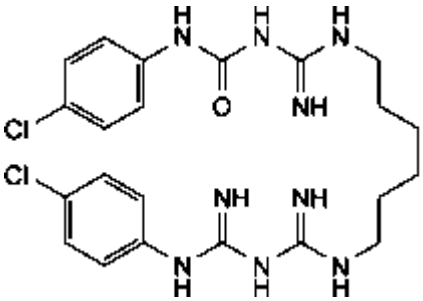


H. N^1,$N^{1\prime}$-[azanediylbis(carbonimidoylazanediylhexane-6,1-diyl)]bis[N^3-(4-chlorophenyl)imidodicarbonimidic diamide],

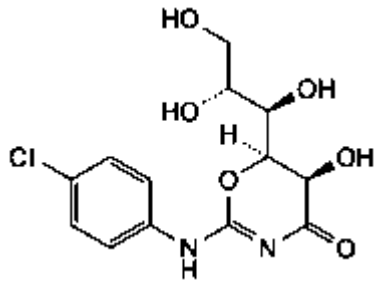
I. unknown structure,



J. 1-(4-chlorophenyl)-5-[6-[[4-[(4-chlorophenyl)amino]-6-[(1*S*,2*R*,3*R*,4*R*)-1,2,3,4,5-pentahydroxypentyl]-1,3,5-triazin-2-yl]amino]hexyl]biguanide,



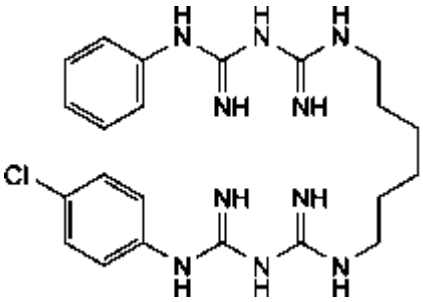
K. *N*-(4-chlorophenyl)-*N*′-[*N*-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]carbamimidoyl]urea,



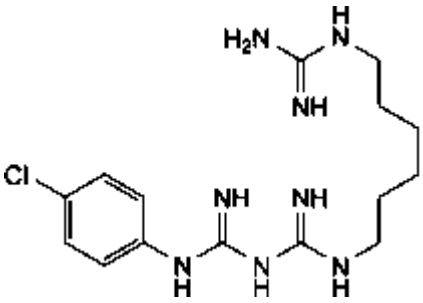
L. (5*R*,6*S*)-2-[(4-chlorophenyl)amino]-5-hydroxy-6-[(1*R*,2*R*)-1,2,3-trihydroxypropyl]-5,6-dihydro-4*H*-1,3-oxazin-4-one,

www.webofpharma.com

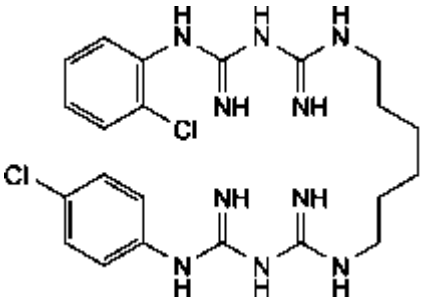
https://thuocngocanh.com/



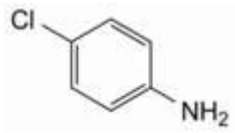
M. N^1-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]-N^3-phenylimidodicarbonimidic diamide,



N. N^1-[6-(carbamimidoylamino)hexyl]-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,



O. N^1-[6-[[*N*-[*N*-(2-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,



P. 4-chloroaniline,

Q. unknown structure.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorhexidine Gluconate Umbilical Cord Gel

General Notices

Action and use

Obstetric antiseptic.

DEFINITION

Chlorhexidine Gluconate Umbilical Cord Gel contains Chlorhexidine Gluconate in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of chlorhexidine gluconate, $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Disperse a quantity of the gel containing the equivalent of 0.5 g of chlorhexidine gluconate in 100 mL of *water*. Further dilute with sufficient *water* to produce a solution containing the equivalent of 0.001% w/v of chlorhexidine gluconate. The *light absorption* of the solution, Appendix II B, in the range 200 to 400 nm exhibits two maxima at 231 nm and 258 nm and two minima at 222 nm and 242 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH of the gel, 5.5 to 7.0, Appendix V L.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

Solution A 0.1 volumes of *trifluoroacetic acid*, 10 volumes of *acetonitrile R1* and 90 volumes of *water*.

(1) To a quantity of the gel containing the equivalent of 80 mg of chlorhexidine gluconate add 50 mL of a mixture of equal volumes of *acetonitrile R1* and *water*. Mix with the aid of ultrasound for at least 30 minutes, with intermittent shaking. Dilute to 100 mL with a mixture of equal volumes of *acetonitrile R1* and *water* and further dilute 1 volume of this solution to 4 volumes with the same solvent mixture. Allow the solution to stand for at least an hour and filter through a 0.45-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.00007% w/v of *4-chloroaniline* (impurity P) in solution A.

www.webofpharma.com

https://thuocngocanh.com/

(4) 0.02% w/v of *chlorhexidine for system suitability EPCRS* in solution A.

(5) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Luna C18 (2) is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use detection wavelengths of 215 nm and 254 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile R1* and 80 volumes of *water*.

Mobile phase B 0.1 volumes of *trifluoroacetic acid*, 10 volumes of *water* and 90 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
32-37	100→80	0→20	linear gradient
37-47	80→70	20→30	linear gradient
47-54	70→100	30→0	linear gradient
54-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to chlorhexidine (retention time about 35 minutes) are: impurity 1, about 0.1; impurity P, about 0.15; impurity 2, about 0.2; impurity L, about 0.23; impurity Q, about 0.24; impurity G, about 0.25; impurity N, about 0.35; impurity B, about 0.36; impurity F, about 0.5; impurity A, about 0.6; impurity H; about 0.85; impurity O, about 0.90; impurity I, about 0.91; impurity J, about 0.96 and impurity K, about 1.4

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3) at 215 nm, the *signal-to noise ratio* of the peak due to impurity P is at least 10;

in the chromatogram obtained with solution (4) at 254 nm, the *resolution* between the peaks due to impurity L and impurity G is at least 3.0;

in the chromatogram obtained with solution (4) at 254 nm, the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity B and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity N.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

At 215 nm

Identify any peak corresponding to impurity P in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (1), the area of any peak corresponding to impurity P is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.35%, with respect to chlorhexidine gluconate).

At 254 nm

Identify any peaks corresponding to impurities A, F, G, H, I + O, J, K and N in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4). Multiply the area of any peak corresponding to impurity F by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity N is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any peak corresponding to impurities J or K is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7% of each);

the area of any peak corresponding to impurity G is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to impurity H is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity A is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to impurities I + O is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to impurity F is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

The total impurity content is not greater than 5.0%.

ASSAY

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared in solution A.

Solution A 0.1 volumes of *trifluoroacetic acid*, 10 volumes of *acetonitrile* and 90 volumes of *water*.

www.webofpharma.com

https://thuocngocanh.com/

(1) Mix with the aid of ultrasound a quantity of the gel containing the equivalent of 80 mg of chlorhexidine gluconate, with 50 mL of a mixture of equal volumes of *acetonitrile* and *water* for at least 30 minutes, with intermittent shaking, and dilute to 100 mL with the same solvent mixture. Dilute 1 volume of this solution to 5 volumes with the solution A and allow the resulting solution to stand for at least 15 minutes. Filter through a 0.45-µm nylon filter.

(2) 0.011% w/v of *chlorhexidine acetate BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (3 cm × 2.1 mm) packed with *end-capped, charged surface, ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material)* (2.5 µm) (Waters Xselect CSH C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

0.1 volumes of *trifluoroacetic acid*, 24 volumes of *acetonitrile* and 76 volumes of *water*.

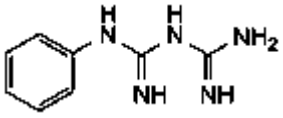
When the chromatograms are recorded under the prescribed conditions, the retention time of chlorhexidine is about 2 minutes.

DETERMINATION OF CONTENT

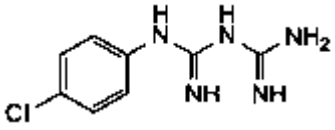
Calculate the content of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$ in the gel from the declared content of $C_{22}H_{30}Cl_2N_{10}$ in *chlorhexidine acetate BPCRS*. Each mg of $C_{22}H_{30}Cl_2N_{10}$ is equivalent to 1.776 mg of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, F, G, H, I, J, K, L, N, O, P and Q listed under Chlorhexidine Gluconate Solution and:



1. 1-phenylbiguanidine



2. 1-(4-chlorophenyl)biguanide

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

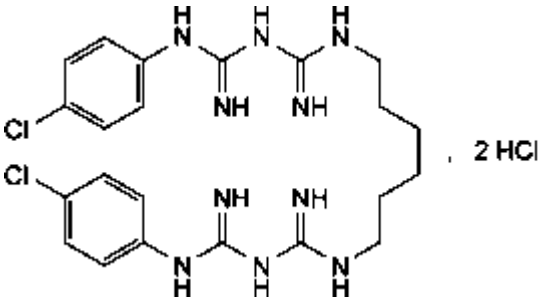
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorhexidine Hydrochloride

General Notices

(Chlorhexidine Dihydrochloride, Ph. Eur. monograph 0659)



$C_{22}H_{32}Cl_4N_{10}$ 578.4 *3697-42-5*

Action and use

Antiseptic.

Ph Eur

DEFINITION

N^1,$N^{1\prime}$-(Hexane-1,6-diyl)bis[N^3-(4-chlorophenyl)imidodicarbonimidic diamide] dihydrochloride.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in propylene glycol, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *chlorhexidine dihydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 5 mg of *chlorhexidine dihydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *water R*, *ethanol (96 per cent) R*, *methylene chloride R* (7:10:40:50 *V/V/V/V*).

Application 5 µL; the volume may be adapted based on the type of plate used.

Development Over 2/3 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

Detection B Treat with *copper sulfate solution R* and examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Impurity P (chloroaniline)

Maximum 300 ppm.

Test solution To 0.20 g add 1 mL of *hydrochloric acid R*, shake for about 30 s, dilute to 30 mL with *water R* and shake until a clear solution is obtained. Add rapidly and with thorough mixing after each addition: 5 mL of a 103 g/L solution of *hydrochloric acid R*, 0.35 mL of *sodium nitrite solution R*, 2 mL of a 50 g/L solution of *ammonium sulfamate R*, 5 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* and 1 mL of *ethanol (96 per cent) R*; transfer quantitatively to a volumetric flask, dilute to 50.0 mL with *water R* and allow to stand for 30 min.

Reference solutions Prepare reference solutions representing respectively 50 ppm, 100 ppm, 200 ppm, 300 ppm and 500 ppm of *chloroaniline R* (impurity P) in the test sample as follows: dilute 1.0 mL, 2.0 mL, 4.0 mL, 6.0 mL and 10.0 mL of a solution containing

www.webofpharma.com

https://thuocngocanh.com/

0.010 g/L of *chloroaniline R* (impurity P) in *dilute hydrochloric acid R* to 20 mL with *water R*. Then, add 10 mL of *water R*. Add rapidly and with thorough mixing after each addition: 5 mL of a 103 g/L solution of *hydrochloric acid R*, 0.35 mL of *sodium nitrite solution R*, 2 mL of a 50 g/L solution of *ammonium sulfamate R*, 5 mL of a 1 g/L solution of *naphthylethylenediamine dihydrochloride R* and 1 mL of *ethanol (96 per cent) R*; transfer each solution quantitatively to a volumetric flask, dilute to 50.0 mL with *water R* and allow to stand for 30 min.

Measure the absorbance (*2.2.25*) of each reference solution at 556 nm and plot a calibration curve.

Measure the absorbance (*2.2.25*) of the test solution at 556 nm. Determine the concentration of chloroaniline from the calibration curve.

Related substances

Liquid chromatography (*2.2.29*). *Store the solutions at a temperature not exceeding 12 °C.*

Test solution Dissolve 0.130 g of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of *chlorhexidine for system suitability CRS* (containing impurities A, B, H, I, K, N and O) in 1.0 mL of mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 20 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *acetonitrile R* and 80 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *water for chromatography R*;

— *mobile phase B*: mix 10 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *water for chromatography R* and 90 volumes of a 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 32	100 → 80	0 → 20
32 - 37	80	20
37 - 47	80 → 70	20 → 30
47 - 54	70	30

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *chlorhexidine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, H, I, K, N and O.

Relative retention With reference to chlorhexidine (retention time = about 35 min): impurity N = about 0.35; impurity B = about 0.36; impurity A = about 0.6; impurity H = about 0.85; impurity O = about 0.90; impurity I = about 0.91; impurity K = about 1.4.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity N.

Limits:

— *impurity H*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity K*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *sum of impurities I and O*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurities A, N*: for each impurity, not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

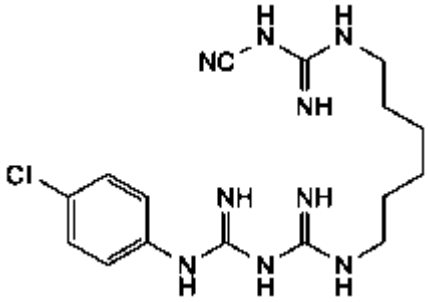
Dissolve 100.0 mg in 5 mL of *anhydrous formic acid R* and add 70 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 14.46 mg of $C_{22}H_{32}Cl_4N_{10}$.

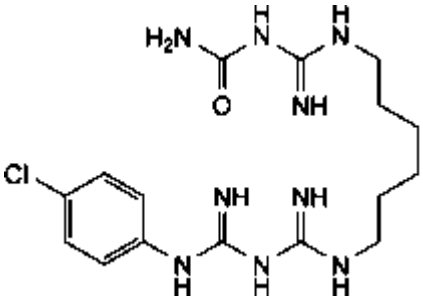
IMPURITIES

Specified impurities *A, H, I, K, N, O, P.*

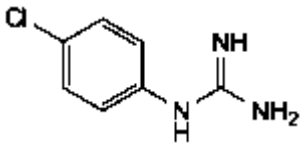
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, E, F, G, M.*



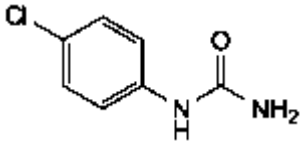
A. N^1-(4-chlorophenyl)-N^3-[6-[(*N*-cyanocarbamimidoyl)amino]hexyl]imidodicarbonimidic diamide,



B. *N*-[*N*-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]carbamimidoyl]urea,



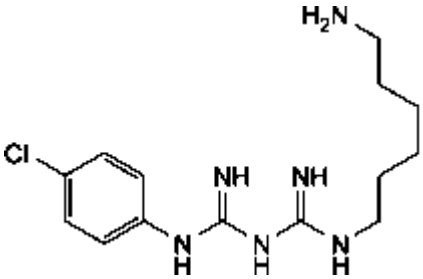
E. *N*-(4-chlorophenyl)guanidine,



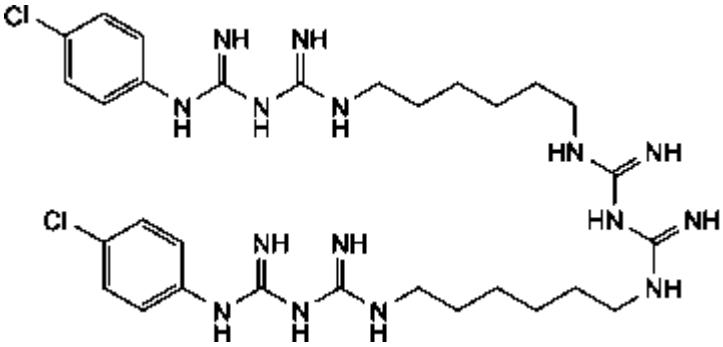
F. *N*-(4-chlorophenyl)urea,

www.webofpharma.com

https://thuocngocanh.com/

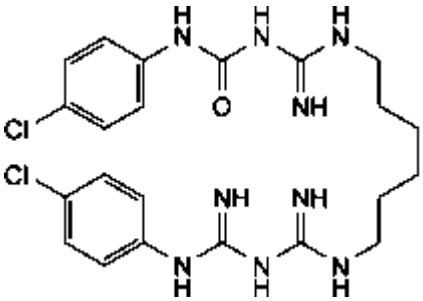


G. N^1-(6-aminohexyl)-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,

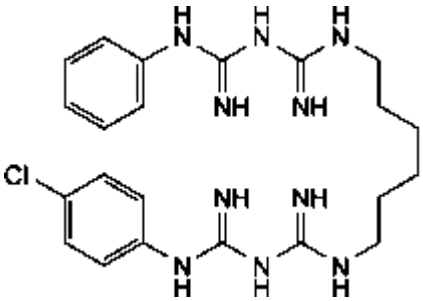


H. N^1,$N^{1\prime}$-[azanediylbis(carbonimidoylazanediylhexane-6,1-diyl)]bis[N^3-(4-chlorophenyl)imidodicarbonimidic diamide],

I. unknown structure,



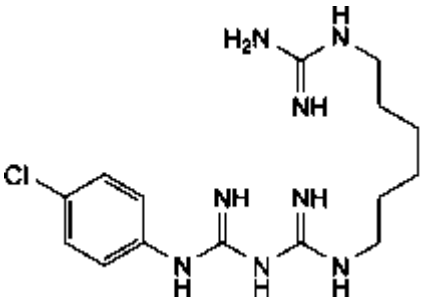
K. *N*-(4-chlorophenyl)-*N*′-[*N*-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]carbamimidoyl]urea,



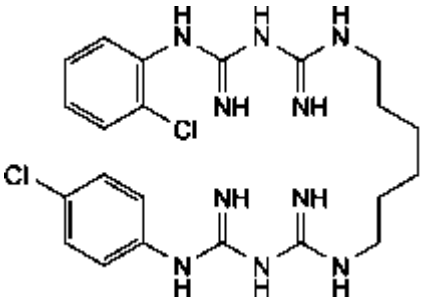
M. N^1-[6-[[*N*-[*N*-(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]-N^3-phenylimidodicarbonimidic diamide,

www.webofpharma.com

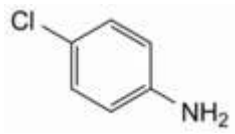
https://thuocngocanh.com/



N. N^1-[6-(carbamimidoylamino)hexyl]-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,



O. N^1-[6-[[*N*-[*N*-(2-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]-N^3-(4-chlorophenyl)imidodicarbonimidic diamide,



P. 4-chloroaniline.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorhexidine Irrigation Solution

General Notices

Action and use

Antiseptic.

DEFINITION

Chlorhexidine Irrigation Solution is a sterile solution of Chlorhexidine Acetate in Water for Irrigation.

The solution complies with the requirements stated under Preparations for Irrigation and with the following requirements.

Content of chlorhexidine acetate, $C_{22}H_{30}Cl_2N_{10},2C_2H_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the peak due to chlorhexidine in the chromatogram obtained with solution (2).

B. To a volume of the irrigation solution containing 2 mg of Chlorhexidine Acetate, add 5 mL of a warm 1% w/v solution *of cetrimide*, 1 mL of 5M *sodium hydroxide* and 1 mL of *bromine water*. A deep red colour is produced.

C. Evaporate or dilute a volume of the irrigation solution containing 6 mg of Chlorhexidine Acetate to about 5 mL. The resulting solution yields reaction B characteristic of *acetates*, Appendix VI.

TESTS

Acidity

pH, 5.0 to 6.5, Appendix V L.

4-Chloroaniline

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

Dissolve 80 mg of *2,6-dimethylaniline* (internal standard) in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 100 mL and dilute 1 volume of this solution to 100 volumes with 0.01M *hydrochloric acid* (solution A).

(1) Shake a volume of the irrigation solution containing 124 mg of Chlorhexidine Acetate with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution*, allow to separate and discard the aqueous layer. Shake the organic layer with *anhydrous sodium sulfate* and filter through silica treated filter paper (Whatman 1PS is suitable), add 100 µL of

www.webofpharma.com

https://thuocngocanh.com/

heptafluorobutyric anhydride and shake for 30 seconds. Allow the solution to stand for 2 minutes, add 5 mL of 0.6M *sodium hydrogen carbonate solution*, shake, allow to separate and use the upper layer.

(2) Add 2 mL of solution A to a volume of the irrigation solution containing 124 mg of Chlorhexidine Acetate, shake with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution* and continue in the same manner as for solution (1) beginning at the words 'allow to separate …'.

REFERENCE SOLUTIONS

Prepare a series of reference solutions in the following manner. Dissolve 25 mg of *4-chloroaniline* in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 200 mL and dilute 1 volume to 10 volumes with the same solvent. To separate 0, 2, 4, 6 and 8 mL volumes of this solution (containing 0, 25, 50, 75 and 100 µg of 4-chloroaniline) add 2 mL of solution A and sufficient *water* to produce 50 mL, shake with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution* and continue in the same manner as for solution (1) beginning at the words 'allow to separate …'.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 15% w/w of *cyanopropylmethylphenyl methyl silicone fluid* (OV-225 is suitable).
(b) Use a flow rate of 50 mL per minute.
(c) Use a column temperature of 190°.
(d) Use an inlet port temperature of 200°.
(e) Use a detector temperature of 270°.
(f) Use *nitrogen* as the carrier gas.
(g) Use an electron capture detector.
(h) Inject 1 µL of each solution.

Inject the reference solutions and construct a calibration curve of the concentration of 4-chloroaniline against the ratio of the area of the peak corresponding to 4-chloroaniline to the area of the peak due to the internal standard.

LIMITS

In the chromatogram obtained with solution (2) determine the ratio of the area of any peak due to 4-chloroaniline to the area of the peak due to the internal standard and hence calculate the content of 4-chloroaniline in the irrigation solution. Not more than 1.5 ppm is detected.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the irrigation solution with *water*, if necessary, to produce a solution containing 0.02% w/v of Chlorhexidine Acetate.
(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.
(3) Dissolve the contents of a vial of *chlorhexidine for system suitability EPCRS* in 10 mL of mobile phase A.
(4) Dilute 1 volume of solution (2) to 10 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Luna C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of a 0.1% v/v solution of *trifluoroacetic acid* in *acetonitrile* and 80 volumes of a 0.1% v/v solution of *trifluoroacetic acid* in *water*.

Mobile phase B 10 volumes of a 0.1% v/v solution of *trifluoroacetic acid* in *water* and 90 volumes of a 0.1% v/v solution of *trifluoroacetic acid* in *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-32	100→80	0→20	linear gradient
32-37	80	20	isocratic
37-47	80→70	20→30	linear gradient
47-54	70	30	isocratic
54-55	70→100	30→0	linear gradient
55-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to chlorhexidine (retention time about 35 minutes) are: impurity L, about 0.23; impurity Q, about 0.24; impurity G, about 0.25; impurity N, about 0.35; impurity B, about 0.36; impurity F, about 0.5; impurity A, about 0.6; impurity H, about 0.85; impurity O, about 0.90; impurity I, about 0.91; impurity J, about 0.96 and impurity K, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity L and impurity G is at least 3.0;

the *peak-to-valley ratio* is at least 2.0, where H_p is the height above the baseline of the peak due to impurity B and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity N.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity N is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak corresponding to impurity H is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity A, J or K is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4% of each);

the sum of the areas of any peaks corresponding to impurities I and O is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to impurity G is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the solution being examined containing 4 mg of Chlorhexidine Acetate with sufficient of the mobile phase to produce 50 mL.
(2) 0.008% w/v of *chlorhexidine acetate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

0.20% w/v of *sodium octanesulfonate* in a mixture of 120 volumes of *glacial acetic acid*, 270 volumes of *water* and 730 volumes of *methanol*.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Determine the weight per mL of the irrigation solution, Appendix V G, and calculate the content of $C_{22}H_{30}Cl_2N_{10},2C_2H_4O_2$ from the declared content of $C_{22}H_{30}Cl_2N_{10}$ in *chlorhexidine acetate BPCRS*. Each mg of $C_{22}H_{30}Cl_2N_{10}$ is equivalent to 1.238 mg of $C_{22}H_{30}Cl_2N_{10},2C_2H_4O_2$.

STORAGE

Chlorhexidine Irrigation Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Chlorhexidine Acetate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorhexidine Mouthwash

General Notices

Action and use

Antiseptic.

DEFINITION

Chlorhexidine Mouthwash contains Chlorhexidine Gluconate Solution in a suitable flavoured and coloured vehicle.

The mouthwash complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of chlorhexidine gluconate, $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the peak due to chlorhexidine in the chromatogram obtained with solution (2).

TESTS

4-Chloroaniline

Not more than 0.3% of the content of chlorhexidine gluconate when determined in the following manner. Dissolve 80 mg of *2,6-dimethylaniline* (internal standard) in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 100 mL and dilute 1 volume of this solution to 100 volumes with 0.01M *hydrochloric acid* (solution A). Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. For solution (1) dilute a volume of the mouthwash containing the equivalent of 25 mg of chlorhexidine gluconate to 50 mL with *water*, shake with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution*, allow to separate and discard the aqueous layer. Shake the organic layer with *anhydrous sodium sulfate* and filter through silica treated filter paper (Whatman 1PS is suitable), add 100 µL of *heptafluorobutyric anhydride* and shake for 30 seconds. Allow the solution to stand for 2 minutes, add 5 mL of 0.6M *sodium hydrogen carbonate solution*, shake, allow to separate and use the upper layer. For solution (2) dilute a volume of the mouthwash containing the equivalent of 25 mg of chlorhexidine gluconate to 50 mL with *water*, add 2 mL of solution A, shake with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution* and continue in the same manner as for solution (1) beginning at the words ‘allow to separate …’. Prepare a series of reference solutions in the following manner. Dissolve 25 mg of *4-chloroaniline* in 1 mL of 1M *hydrochloric acid* with the aid of ultrasound, add sufficient *water* to produce 200 mL and dilute 1 volume to 10 volumes with the same solvent. To separate 0, 2, 4, 6 and 8 mL volumes of this solution (containing 0, 25, 50, 75 and 100 µg of 4-chloroaniline) add 2 mL of solution A and

www.webofpharma.com

https://thuocngocanh.com/

sufficient *water* to produce 50 mL, shake with 20 mL of a mixture of 20 volumes of *ether* and 80 volumes of *hexane* and 5 mL of 0.6M *sodium hydrogen carbonate solution* and continue in the same manner as for solution (1) beginning at the words 'allow to separate …'.

The chromatographic procedure may be carried out using (a) a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 15% w/w of cyanopropylmethylphenyl methyl silicone fluid (OV-225 is suitable) at a temperature of 190° with the inlet port at 200° and the detector at 270°, (b) *nitrogen* as the carrier gas at a flow rate of 50 mL per minute and (c) an electron capture detector.

Inject the reference solutions and construct a calibration curve of the concentration of 4-chloroaniline against the ratio of the area of the peak corresponding to 4-chloroaniline to the area of the peak due to the internal standard. In the chromatogram obtained with solution (2) determine the ratio of the area of any peak due to 4-chloroaniline to the area of the peak due to the internal standard and hence calculate the content of 4-chloroaniline in the mouthwash with respect to the labelled content of chlorhexidine gluconate.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute a quantity of the mouthwash with sufficient of the mobile phase to produce a solution containing 0.01% w/v of chlorhexidine gluconate. Solution (2) contains 0.008% w/v of *chlorhexidine acetate BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a solution containing 2 g of *sodium octanesulfonate* in a mixture of 120 mL of *glacial acetic acid*, 270 mL of *water* and 730 mL of *methanol* and (c) a detection wavelength of 254 nm.

Equilibrate the column with the mobile phase for at least 1 hour.

Calculate the content of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$ from the declared content of $C_{22}H_{30}Cl_2N_{10}$ in *chlorhexidine acetate BPCRS*. Each mg of $C_{22}H_{30}Cl_2N_{10}$, is equivalent to 1.776 mg of $C_{22}H_{30}Cl_2N_{10},2C_6H_{12}O_7$.

STORAGE

Chlorhexidine Mouthwash should be protected from light.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorinated Lime

General Notices

Action and use

Disinfectant.

DEFINITION

Chlorinated Lime contains not less than 30.0% w/w of available chlorine, Cl.

CHARACTERISTICS

A dull white powder.

Partly soluble in *water* and in *ethanol (96%)*.

IDENTIFICATION

A. Evolves chlorine copiously on the addition of 2M *hydrochloric acid*.

B. When shaken with *water* and filtered, the filtrate yields reaction C characteristic of *calcium salts* and reaction A characteristic of *chlorides*, Appendix VI.

ASSAY

Triturate 4 g with successive small quantities of *water*, dilute to 1000 mL with *water* and shake thoroughly. Mix 100 mL of the resulting suspension with a solution containing 3 g of *potassium iodide* in 100 mL of *water*, acidify with 5 mL of 6M *acetic acid* and titrate the liberated iodine with 0.1M *sodium thiosulfate VS*. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 3.545 mg of available chlorine, Cl.

STORAGE

On exposure to air Chlorinated Lime becomes moist and gradually decomposes, carbon dioxide being absorbed and chlorine evolved.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

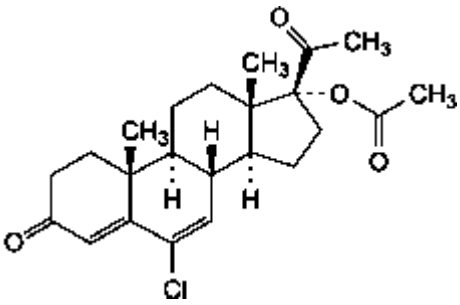
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlormadinone Acetate

General Notices

(Ph. Eur. monograph 2702)



$C_{23}H_{29}ClO_4$ 404.9 *302-22-7*

Action and use

Progestogen.

Ph Eur

DEFINITION

6-Chloro-3,20-dioxopregna-4,6-dien-17-yl acetate.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetonitrile, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *chlormadinone acetate CRS*.

TESTS

Specific optical rotation (*2.2.7*)

-14.0 to -10.0 (dried substance).

Dissolve 0.200 g in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 20 mg of the substance to be examined in mobile phase B and dilute to 10.0 mL with mobile phase B.

Test solution (b) Dissolve 10.0 mg of the substance to be examined in mobile phase B and dilute to 20.0 mL with mobile phase B.

Reference solution (a) Dissolve 4 mg of *chlormadinone acetate for system suitability CRS* (containing impurities A, B, E and K) in mobile phase B and dilute to 2.0 mL with mobile phase B.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with mobile phase B. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase B.

Reference solution (c) Dissolve 5.0 mg of *chlormadinone acetate impurity G CRS* in mobile phase B and dilute to 50.0 mL with mobile phase B. Dilute 1.0 mL of the solution to 50.0 mL with mobile phase B.

Reference solution (d) Dissolve 10.0 mg of *chlormadinone acetate CRS* in mobile phase B and dilute to 20.0 mL with mobile phase B.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (3.5 µm).

Mobile phase:

— *mobile phase A*: *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	60	40
8 - 30	60 → 5	40 → 95
30 - 33	5	95

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 236 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *chlormadinone acetate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, E and K; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity G.

Relative retention With reference to chlormadinone acetate (retention time = about 15 min): impurity K = about 0.75; impurity G = about 0.80; impurity A = about 0.95; impurity E = about 1.04; impurity B = about 1.2.

System suitability:

— *signal-to-noise ratio*: minimum 35 for the principal peak in the chromatogram obtained with reference solution (b);

— *peak-to-valley ratio*: minimum 1.6, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to chlormadinone acetate in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity K by 1.7;

— for impurities E, B and K, use the concentration of chlormadinone acetate in reference solution (b);

— for impurities other than E, B and K, use the concentration of impurity G in reference solution (c).

Limits:

— *impurity B*: maximum 0.2 per cent;

— *impurities A, E, G, K*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (45:55 *V/V*).

Injection Test solution (b) and reference solution (d).

Run time Twice the retention time of chlormadinone acetate.

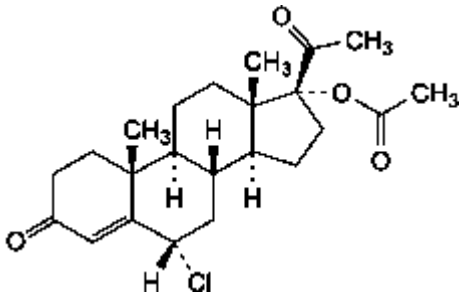
Retention time Chlormadinone acetate = about 12 min.

Calculate the percentage content of $C_{23}H_{29}ClO_4$ taking into account the assigned content of *chlormadinone acetate CRS*.

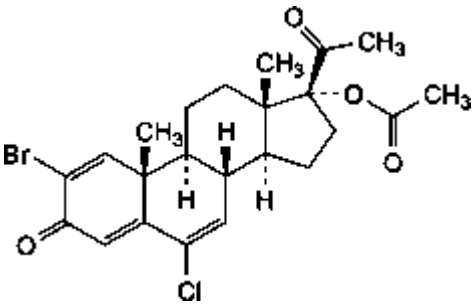
IMPURITIES

Specified impurities *A, B, E, G, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, F, H, I, J, L.*



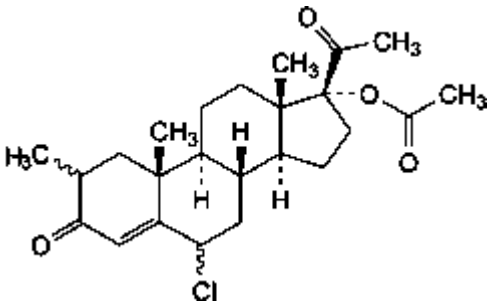
A. 6α-chloro-3,20-dioxopregn-4-en-17-yl acetate,



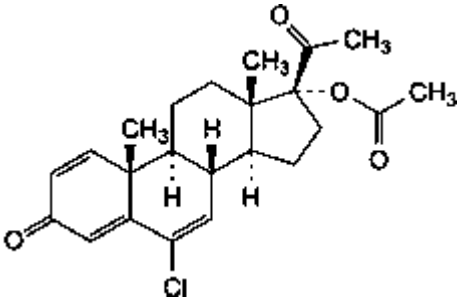
B. 2-bromo-6-chloro-3,20-dioxopregna-1,4,6-trien-17-yl acetate,

www.webofpharma.com

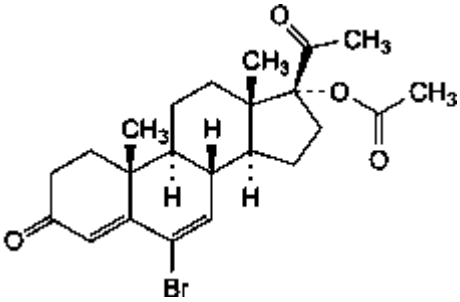
https://thuocngocanh.com/



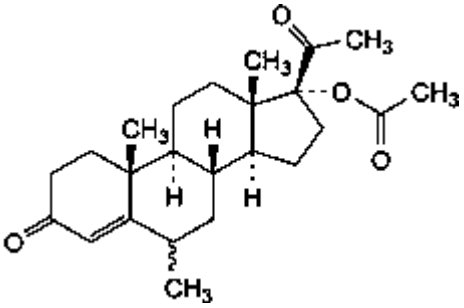
C. 6ξ-chloro-2ξ-methyl-3,20-dioxopregn-4-en-17-yl acetate,



D. 6-chloro-3,20-dioxopregna-1,4,6-trien-17-yl acetate,



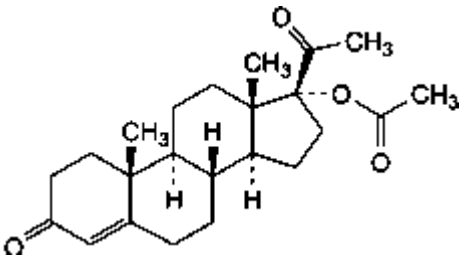
E. 6-bromo-3,20-dioxopregna-4,6-dien-17-yl acetate,



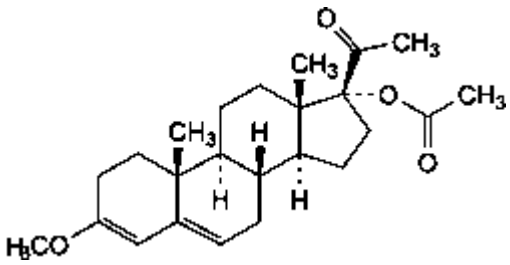
F. 6ξ-methyl-3,20-dioxopregn-4-en-17-yl acetate,

www.webofpharma.com

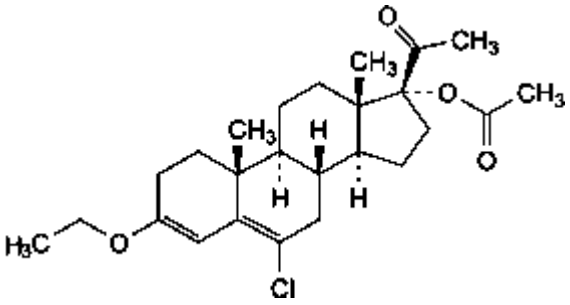
https://thuocngocanh.com/



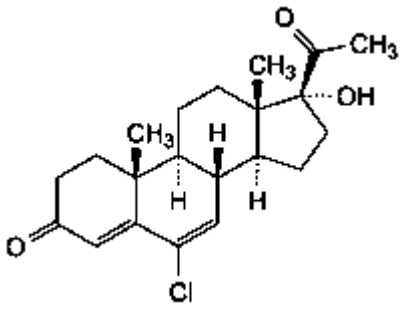
G. 3,20-dioxopregn-4-en-17-yl acetate,



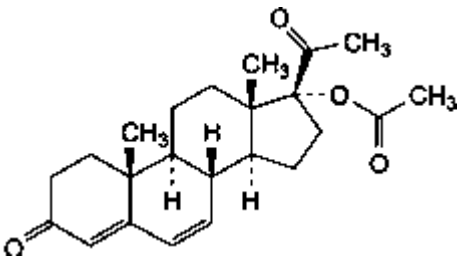
H. 3-methoxy-20-oxopregna-3,5-dien-17-yl acetate,



I. 6-chloro-3-ethoxy-20-oxopregna-3,5-dien-17-yl acetate,



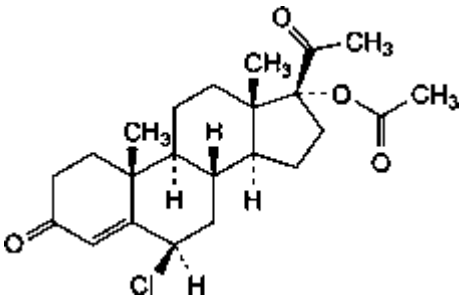
J. 6-chloro-17-hydroxypregna-4,6-diene-3,20-dione,



K. 3,20-dioxopregna-4,6-dien-17-yl acetate,

www.webofpharma.com

https://thuocngocanh.com/



L. 6β-chloro-3,20-dioxopregn-4-en-17-yl acetate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

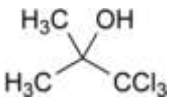
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorobutanol

General Notices

Anhydrous Chlorobutanol

(Ph. Eur. monograph 0382)



$C_4H_7Cl_3O$ 177.5 *57-15-8*

Action and use

Disinfectant preservative.

Ph Eur

DEFINITION

1,1,1-Trichloro-2-methylpropan-2-ol.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, sublimes readily.

Solubility

Slightly soluble in water, very soluble in ethanol (96 per cent), soluble in glycerol (85 per cent).

mp

About 95 °C (without previous drying).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *chlorobutanol CRS*.

B. Water (see Tests).

TESTS

Solution S

Dissolve 5 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Acidity

To 4 mL of solution S add 15 mL of *ethanol (96 per cent) R* and 0.1 mL of *bromothymol blue solution R1*. Not more than 1.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Impurities A and B

Head-space gas chromatography (*2.2.28*).

Solvent mixture *water R*, *dimethylformamide R* (40:60 *V/V*).

Test solution Introduce 2.000 g of the substance to be examined into a vial, add 5.0 mL of the solvent mixture and close the vial immediately.

Reference solution (a) Dissolve 60.0 mg of *chloroform R* (impurity A) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Shake well. Dilute 4.0 mL of the solution to 200.0 mL with the solvent mixture and transfer 5.0 mL to an injection vial.

Reference solution (b) Dissolve 0.500 g of *acetone R* (impurity B) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Shake well.

Reference solution (c) Dilute 8.0 mL of reference solution (b) to 200.0 mL with the solvent mixture and transfer 5.0 mL to an injection vial.

Reference solution (d) Dissolve 50.0 mg of *2-propanol R* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Shake well. Mix 8.0 mL of the solution and 8.0 mL of reference solution (b), dilute to 200.0 mL with the solvent mixture and transfer 5.0 mL to an injection vial.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 3 µm).

www.webofpharma.com

https://thuocngocanh.com/

Carrier gas *nitrogen R*.

Flow rate 1.7 mL/min.

Split ratio 1:3.

Static head-space conditions that may be used:

— *equilibration temperature*: 90 °C;

— *equilibration time*: 20 min;

— *pressurisation time*: 30 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 25	40
	25 - 37	40 → 220
	37 - 42	220
Injection port		220
Detector		230

Detection Flame ionisation.

Injection 1.0 mL of the test solution and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (d) to identify the peak due to 2-propanol.

Relative retention With reference to impurity B (retention time = about 14 min): 2-propanol = about 1.1; impurity A = about 2.0.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurity B and 2-propanol.

Calculation of contents:

— for impurity A, use the concentration of impurity A in reference solution (a);

— for impurity B, use the concentration of impurity B in reference solution (c).

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity B*: maximum 0.10 per cent;

— *impurity A*: maximum 60 ppm.

Chlorides (*2.4.4*)

Maximum 300 ppm.

Dissolve 0.17 g in 5 mL of *ethanol (96 per cent) R* and dilute to 15 mL with *water R*. When preparing the standard, replace the 5 mL of *water R* by 5 mL of *ethanol (96 per cent) R*.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 2.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 50.0 mg in 20 mL of *ethanol (96 per cent) R* in a 50 mL centrifuge tube. Add 10 mL of *dilute sodium hydroxide solution R*, cap tightly and heat in a water-bath for 10 min. Cool and transfer quantitatively to a titration vessel using 100 mL of *water R*. Add 20 mL of *dilute nitric acid R* and titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

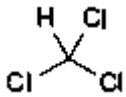
1 mL of *0.1 M silver nitrate* is equivalent to 5.92 mg of $C_4H_7Cl_3O$.

STORAGE

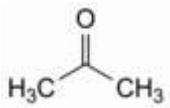
In an airtight container.

IMPURITIES

Specified impurities *A, B.*



A. trichloromethane (chloroform),



B. propan-2-one (acetone).

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

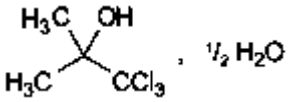
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorobutanol Hemihydrate

General Notices

(Ph. Eur. monograph 0383)

NOTE: *The name Chlorobutanol was formerly used in the United Kingdom*



$C_4H_7Cl_3O,½H_2O$ 186.5 *6001-64-5*

Action and use

Disinfectant preservative.

Ph Eur

DEFINITION

1,1,1-Trichloro-2-methylpropan-2-ol hemihydrate.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, sublimes readily.

Solubility

Slightly soluble in water, very soluble in ethanol (96 per cent), soluble in glycerol (85 per cent).

mp

About 78 °C (without previous drying).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *chlorobutanol hemihydrate CRS*.

B. Water (see Tests).

TESTS

Solution S

Dissolve 5 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Acidity

To 4 mL of solution S add 15 mL of *ethanol (96 per cent) R* and 0.1 mL of *bromothymol blue solution R1*. Not more than 1.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Impurities A and B

Head-space gas chromatography (*2.2.28*).

Solvent mixture *water R*, *dimethylformamide R* (40:60 *V/V*).

Test solution Introduce 2.000 g of the substance to be examined into a vial, add 5.0 mL of the solvent mixture and close the vial immediately.

Reference solution (a) Dissolve 60.0 mg of *chloroform R* (impurity A) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Shake well. Dilute 4.0 mL of the solution to 200.0 mL with the solvent mixture and transfer 5.0 mL to an injection vial.

Reference solution (b) Dissolve 0.500 g of *acetone R* (impurity B) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Shake well.

Reference solution (c) Dilute 8.0 mL of reference solution (b) to 200.0 mL with the solvent mixture and transfer 5.0 mL to an injection vial.

Reference solution (d) Dissolve 50.0 mg of *2-propanol R* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Shake well. Mix 8.0 mL of the solution and 8.0 mL of reference solution (b), dilute to 200.0 mL with the solvent mixture and transfer 5.0 mL to an injection vial.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 3 µm).

www.webofpharma.com

https://thuocngocanh.com/

Carrier gas nitrogen R.

Flow rate 1.7 mL/min.

Split ratio 1:3.

Static head-space conditions that may be used:

— *equilibration temperature*: 90 °C;

— *equilibration time*: 20 min;

— *pressurisation time*: 30 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 25	40
	25 - 37	40 → 220
	37 - 42	220
Injection port		220
Detector		230

Detection Flame ionisation.

Injection 1.0 mL of the test solution and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (d) to identify the peak due to 2-propanol.

Relative retention With reference to impurity B (retention time = about 14 min): 2-propanol = about 1.1; impurity A = about 2.0.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurity B and 2-propanol.

Calculation of contents:

— for impurity A, use the concentration of impurity A in reference solution (a);

— for impurity B, use the concentration of impurity B in reference solution (c).

Limits:

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *impurity B*: maximum 0.10 per cent;

— *impurity A*: maximum 60 ppm.

Chlorides (*2.4.4*)

Maximum 100 ppm.

To 1 mL of solution S add 4 mL of *ethanol (96 per cent) R* and dilute to 15 mL with *water R*. When preparing the standard, replace the 5 mL of *water R* by 5 mL of *ethanol (96 per cent) R*.

Water (*2.5.12*)

4.5 per cent to 5.5 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 50.0 mg in 20 mL of *ethanol (96 per cent) R* in a 50 mL centrifuge tube. Add 10 mL of *dilute sodium hydroxide solution R*, cap tightly and heat in a water-bath for 10 min. Cool and transfer quantitatively to a titration vessel using 100 mL of *water R*. Add 20 mL of *dilute nitric acid R* and titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

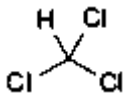
1 mL of *0.1 M silver nitrate* is equivalent to 5.92 mg of $C_4H_7Cl_3O$.

STORAGE

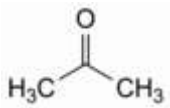
In an airtight container.

IMPURITIES

Specified impurities *A, B.*



A. trichloromethane (chloroform),



B. propan-2-one (acetone).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

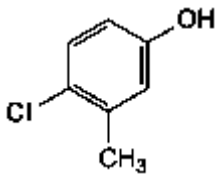
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorocresol

General Notices

(Ph. Eur. monograph 0384)



C_7H_7ClO 142.6 *59-50-7*

Action and use

Antiseptic; antimicrobial preservative.

Ph Eur

DEFINITION

4-Chloro-3-methylphenol.

Content

98.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or compacted crystalline masses supplied as pellets or colourless or white crystals.

Solubility

Slightly soluble in water, very soluble in ethanol (96 per cent), freely soluble in fatty oils. It dissolves in solutions of alkali hydroxides.

IDENTIFICATION

A. Melting point (2.2.14): 64 °C to 67 °C.

B. To 0.1 g add 0.2 mL of *benzoyl chloride R* and 0.5 mL of *dilute sodium hydroxide solution R*. Shake vigorously until a white, crystalline precipitate is formed. Add 5 mL of *water R* and filter. The precipitate, recrystallised from 5 mL of *methanol R* and dried at 70 °C, melts (2.2.14) at 85 °C to 88 °C.

C. To 5 mL of solution S (see Tests) add 0.1 mL of *ferric chloride solution R1*. A bluish colour is produced.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

To 3.0 g, finely powdered, add 60 mL of *carbon dioxide-free water R*, shake for 2 min and filter.

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 1.25 g in *ethanol (96 per cent) R* and dilute to 25 mL with the same solvent.

Acidity

To 10 mL of solution S add 0.1 mL of *methyl red solution R*. The solution is orange or red. Not more than 0.2 mL of *0.01 M sodium hydroxide* is required to produce a pure yellow colour.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution Dissolve 1.0 g of the substance to be examined in *acetone R* and dilute to 100 mL with the same solvent.

Reference solution Dilute 1.0 mL of the test solution to 100.0 mL with *acetone R*. Dilute 5.0 mL of this solution to 100.0 mL with *acetone R*.

Column:

— *material*: glass;

— *size*: *l* = 1.80 m, Ø = 3-4 mm;

— *stationary phase*: *silanised diatomaceous earth for gas chromatography R* impregnated with 3-5 per cent *m/m* of *phenyl(50)methyl(50)polysiloxane R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 125 °C;

— *injection port*: 210 °C;

— *detector*: 230 °C.

Detection Flame ionisation.

www.webofpharma.com

https://thuocngocanh.com/

Run time 3 times the retention time of chlorocresol.

Retention time Chlorocresol = about 8 min.

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Non-volatile matter

Maximum 0.1 per cent.

Evaporate 2.0 g to dryness on a water-bath and dry the residue at 100-105 °C. The residue weighs not more than 2 mg.

ASSAY

In a ground-glass-stoppered flask, dissolve 70.0 mg in 30 mL of *glacial acetic acid R*. Add 25.0 mL of *0.0167 M potassium bromate*, 20 mL of a 150 g/L solution of *potassium bromide R* and 10 mL of *hydrochloric acid R*. Allow to stand protected from light for 15 min. Add 1 g of *potassium iodide R* and 100 mL of *water R*. Titrate with *0.1 M sodium thiosulfate*, shaking vigorously and using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration.

1 mL of *0.0167 M potassium bromate* is equivalent to 3.565 mg of C_7H_7ClO.

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

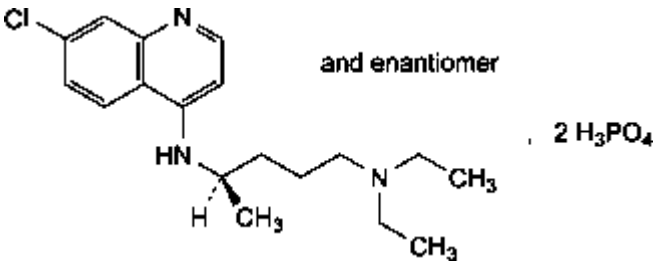
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Chloroquine Phosphate

General Notices

(Ph. Eur. monograph 0544)



$C_{18}H_{32}ClN_3O_8P_2$ 515.9 *50-63-5*

Action and use

Antiprotozoal (malaria).

Preparation

Chloroquine Phosphate Tablets

Ph Eur

DEFINITION

Chloroquine phosphate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of N^4-(7-chloroquinolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine bis(dihydrogen phosphate), calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, hygroscopic, freely soluble in water, very slightly soluble in ethanol (96 per cent) and in methanol.

It exists in 2 forms, one of which melts at about 195 °C and the other at about 218 °C.

IDENTIFICATION

First identification: B, D.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, C, D.

A. Dissolve 0.100 g in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *water R*. Examined between 210 nm and 370 nm (*2.2.25*), the solution shows absorption maxima at 220 nm, 235 nm, 256 nm, 329 nm and 342 nm. The specific absorbances at the maxima are respectively 600 to 660, 350 to 390, 300 to 330, 325 to 355 and 360 to 390.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with the base isolated from *chloroquine sulfate CRS*. Record the spectra using solutions prepared as follows: dissolve separately 0.1 g of the substance to be examined and 80 mg of the reference substance in 10 mL of *water R*, add 2 mL of *dilute sodium hydroxide solution R* and shake with 2 quantities, each of 20 mL, of *methylene chloride R*; combine the organic layers, wash with *water R*, dry over *anhydrous sodium sulfate R*, evaporate to dryness and dissolve the residues separately, each in 2 mL of *methylene chloride R*.

C. Dissolve 25 mg in 20 mL of *water R* and add 8 mL of *picric acid solution R1*. The precipitate, washed with *water R*, with *alcohol R* and finally with *methylene chloride R*, melts (*2.2.14*) at 206-209 °C.

D. Dissolve 0.1 g in 10 mL of *water R*, add 2 mL of *dilute sodium hydroxide solution R* and shake with 2 quantities, each of 20 mL, of *methylene chloride R*. The aqueous layer, acidified by the addition of *nitric acid R*, gives reaction (b) of phosphates (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 or GY_5 (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 3.8 to 4.3.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution Dissolve 0.50 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 1 mL of the test solution to 100 mL with *water R*.

Reference solution (b) Dilute 5 mL of reference solution (a) to 10 mL with *water R*.

Apply to the plate 2 µL of each solution. Develop over a path of 12 cm using a mixture of 10 volumes of *diethylamine R*, 40 volumes of *cyclohexane R* and 50 volumes of *chloroform R*. Allow the plate to dry in air. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1.0 per cent) and not more than one such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Loss on drying (*2.2.32*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.200 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.79 mg of $C_{18}H_{32}ClN_3O_8P_2$.

STORAGE

In an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloroquine Phosphate Tablets

General Notices

Action and use

Antiprotozoal (malaria).

DEFINITION

Chloroquine Phosphate Tablets contain Chloroquine Phosphate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of chloroquine phosphate, $C_{18}H_{26}ClN_3,2H_3PO_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powdered tablets containing 0.1 g of Chloroquine Phosphate in a mixture of 10 mL of *water* and 2 mL of 2M *sodium hydroxide* and extract with two 20-mL quantities of *chloroform*. Wash the chloroform extracts with *water*, dry with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 2 mL of *chloroform IR*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of chloroquine *(RS 054)*.

B. Extract a quantity of the powdered tablets containing 25 mg of Chloroquine Phosphate with 20 mL of *water*, filter and add 8 mL of *picric acid solution R1* to the filtrate. The *melting point* of the precipitate, after washing successively with *water*, *ethanol (96%)* and *ether*, is about 207°, Appendix V A.

C. Extract a quantity of the powdered tablets containing 0.5 g of Chloroquine Phosphate with 25 mL of *water* and filter. To the filtrate add 2.5 mL of 5M *sodium hydroxide* and extract with three 10 mL quantities of *ether*. The aqueous layer, after neutralisation with 2M *nitric acid*, yields the reactions characteristic *of phosphates*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using as the medium 900 mL of *0.1M hydrochloric acid* and rotating the basket at 100 revolutions per minute. Withdraw a sample of 10 mL of the medium. Measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted if necessary, at the maximum at 344 nm, Appendix II B. Calculate the total content of chloroquine phosphate, $C_{18}H_{26}ClN_3,2H_3PO_4$, in the medium taking 371 as the value of A(1%, 1 cm) at the maximum at 344 nm.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 50 volumes of *chloroform*, 40 volumes of *cyclohexane* and 10 volumes of *diethylamine* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 1 g of Chloroquine Phosphate with 20 mL of *water* for 30 minutes, centrifuge and use the supernatant liquid; if necessary filter through a glass fibre paper. For solution (2) dilute 1 mL of solution (1) to 100 mL with *water*. For solution (3) dilute 25 mL of solution (2) to 50 mL with *water*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3).

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.5 g of Chloroquine Phosphate in 20 mL of 1M *sodium hydroxide* and extract with four 25-mL quantities of *chloroform*. Combine the chloroform extracts and evaporate to a volume of about 10 mL. Add 40 mL of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 25.79 mg of $C_{18}H_{26}ClN_3,2H_3PO_4$.

250 mg of Chloroquine Phosphate is approximately equivalent to 155 mg of chloroquine.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

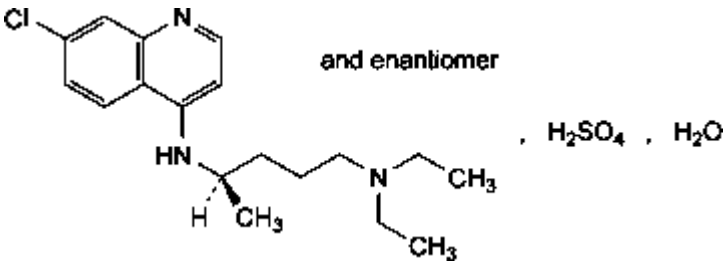
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloroquine Sulfate

General Notices

Chloroquine Sulphate

(Ph. Eur. monograph 0545)



$C_{18}H_{28}ClN_3O_4S,H_2O$ 436.0

Action and use

Antiprotozoal (malaria).

Preparation

Chloroquine Sulfate Tablets

Ph Eur

DEFINITION

Chloroquine sulfate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of N^4-(7-chloroquinolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine sulfate, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder, freely soluble in water and in methanol, very slightly soluble in ethanol (96 per cent).

It melts at about 208 °C (instantaneous method).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Dissolve 0.100 g in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *water R*. Examined between 210 nm and 370 nm (*2.2.25*), the solution shows absorption maxima at 220 nm, 235 nm, 256 nm, 329 nm and 342 nm. The specific absorbances at the maxima are respectively 730 to 810, 430 to 470, 370 to 410, 400 to 440 and 430 to 470.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with the base isolated from *chloroquine sulfate CRS*. Record the spectra using solutions prepared as follows: dissolve separately 0.1 g of the substance to be examined and of the reference substance in 10 mL of *water R*, add 2 mL of *dilute sodium hydroxide solution R* and shake with 2 quantities, each of 20 mL, of *methylene chloride R*; combine the organic layers, wash with *water R*, dry over *anhydrous sodium sulfate R*, evaporate to dryness and dissolve the residues separately each in 2 mL of *methylene chloride R*.

C. Dissolve 25 mg in 20 mL of *water R* and add 8 mL of *picric acid solution R1*. The precipitate, washed with *water R*, with *ethanol (96 per cent) R* and finally with *ether R*, melts (*2.2.14*) at 206 °C to 209 °C.

D. It gives reaction (a) of sulfates (*2.3.1*).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 or GY_5 (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 4.0 to 5.0.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution Dissolve 0.50 g of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dilute 1 mL of the test solution to 100 mL with *water R*.

Reference solution (b) Dilute 5 mL of reference solution (a) to 10 mL with *water R*.

Apply separately to the plate 2 µL of each solution. Develop over a path of 12 cm using a mixture of 10 volumes of *diethylamine R*, 40 volumes of *cyclohexane R* and 50 volumes of *methylene chloride R*. Allow the plate to dry in air. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1.0 per cent) and not more than one such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Water (*2.5.12*)

3.0 per cent to 5.0 per cent, determined on 0.500 g.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 41.8 mg of $C_{18}H_{28}ClN_3O_4S$.

STORAGE

Store in an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloroquine Sulfate Tablets

General Notices

Chloroquine Sulphate Tablets

Action and use

Antiprotozoal (malaria).

DEFINITION

Chloroquine Sulfate Tablets contain Chloroquine Sulfate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of chloroquine sulfate, $C_{18}H_{26}ClN_3,H_2SO_4,H_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powdered tablets containing 0.1 g of Chloroquine Sulfate in a mixture of 10 mL of *water* and 2 mL of 2M *sodium hydroxide* and extract with two 20-mL quantities of *chloroform*. Wash the chloroform extracts with *water*, dry with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 2 mL of *chloroform IR*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of chloroquine *(RS 054)*.

B. Shake a quantity of the powdered tablets containing 0.1 g of Chloroquine Sulfate with 10 mL of *water* and 1 mL of 2M *hydrochloric acid* and filter. To the filtrate add 1 mL of *barium chloride solution*. A white precipitate is produced.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 344 nm, Appendix II B using 0.01M *hydrochloric acid*

www.webofpharma.com

https://thuocngocanh.com/

in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of chloroquine sulfate, $C_{18}H_{26}ClN_3,H_2SO_4,H_2O$, in the medium taking 450 as the value of A(1%, 1 cm) at the maximum at 344 nm.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 2.0 g of Chloroquine Sulfate with 50 mL of *water* for 30 minutes, centrifuge and use the supernatant liquid; if necessary filter through a glass fibre paper.

(2) Dilute 1 mL of solution (1) to 100 mL with *water*.

(3) Dilute 25 mL of solution (2) to 50 mL with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *diethylamine*, 40 volumes of *cyclohexane* and 50 volumes of *chloroform*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3).

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.5 g of Chloroquine Sulfate in 20 mL of 1M *sodium hydroxide* and extract with four 25-mL quantities of *chloroform*. Combine the chloroform extracts and evaporate to a volume of about 10 mL. Add 40 mL of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 20.90 mg of $C_{18}H_{26}ClN_3,H_2SO_4$.

200 mg of Chloroquine Sulfate is approximately equivalent to 146 mg of chloroquine.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

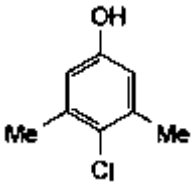
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloroxylenol

General Notices



C_8H_9ClO 156.6 *88-04-0*

Action and use

Antiseptic.

Preparation

Chloroxylenol Solution

DEFINITION

Chloroxylenol is 4-chloro-3,5-xylenol. It contains not less than 98.0% and not more than 103.0% of C_8H_9ClO.

CHARACTERISTICS

White or cream crystals or crystalline powder. It is volatile in steam.

Very slightly soluble in *water*; freely soluble in *ethanol (96%)*; soluble in *ether*, in terpenes and in fixed oils. It dissolves in solutions of the alkali hydroxides.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of chloroxylenol *(RS 055)*.

TESTS

Melting point

114° to 116°, Appendix V A.

Tetrachloroethylene

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. Prepare a 0.2% v/v solution of *butanol* (internal standard) in *methanol* (solution A).

(1) To 4 g of the substance being examined, add 5 mL of solution A and dilute to 25 mL with *methanol*.

(2) To 5 mL of a 0.2% v/v solution of *tetrachloroethylene* in *methanol*, add 5 mL of solution A and dilute to 25 mL with *methanol* (equivalent to 0.06488% w/v of *tetrachloroethylene* in *methanol*).

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a 1 µm film of *polyethylene glycol 20,000* (RH-Wax is suitable).

(b) Use *hydrogen* as the carrier gas at 2 mL per minute.

(c) Use the gradient conditions described below.

(d) Use an inlet temperature of 240°.

(e) Use a flame ionisation detector at a temperature of 280°.

(f) Inject 0.5 µL of each solution.

(g) Use a split ratio of 1:20.

Time (Minutes)	Temperature	Comment
0 - 4	70°	isothermal
4 - 5	70°→210°	linear increase
5 - 15	210	isothermal
15 - 18	210°→70°	linear gradient
18 - 20	70°	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to tetrachloroethylene and the internal standard is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1), the ratio of any peak due to tetrachloroethylene to that of the internal standard is not greater than the corresponding ratio obtained in the chromatogram obtained with solution (2) (0.4%).

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions in *chloroform*.

(1) 2.0% w/v of the substance being examined.

(2) 2.0% w/v of the substance being examined and 0.040% w/v of *4-chloro-o-cresol* (internal standard).

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed diatomaceous support* (80 to 100 mesh) coated with 3% w/w of polyethylene glycol (Carbowax 20M is suitable).

(b) Use *nitrogen* as the carrier gas at 40 mL per minute.

(c) Use isothermal conditions maintained at 160°.

(d) Use an inlet temperature of 200°.

(e) Use a flame ionisation detector at a temperature of 300°.

(f) Inject 1 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to chloroxylenol and 4-chloro-o-cresol is at least 1.5

LIMITS

In the chromatogram obtained with solution (2) the sum of the areas of any *secondary peaks* is not greater than the area of the peak due to the internal standard.

ASSAY

Dissolve 70 mg in 30 mL of *glacial acetic acid*, add 25 mL of *0.0167M potassium bromate VS*, 20 mL of a 15% w/v solution of *potassium bromide* and 10 mL of *hydrochloric acid*, stopper the flask and allow to stand protected from light for 15 minutes. Add 1 g of *potassium iodide* and 100 mL of *water* and titrate with 0.1M *sodium thiosulfate VS*, shaking vigorously and using 1 mL of *starch solution*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of potassium bromate required. Each mL of *0.0167M potassium bromate VS* is equivalent to 3.915 mg of C_8H_9ClO.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chloroxylenol Solution

General Notices

Chloroxylenol Cutaneous Solution

Action and use

Antiseptic.

DEFINITION

Chloroxylenol Solution is a *cutaneous solution*.

Chloroxylenol	50.0 g
Potassium Hydroxide	13.6 g
Oleic Acid	7.5 mL
Virgin Castor Oil	63.0 g
Terpineol	100 mL
Ethanol (96 per cent)	200 mL
Purified Water, freshly boiled and cooled	Sufficient to produce 1000 mL

In making Chloroxylenol Solution, the Ethanol (96 per cent) may be replaced by Industrial Methylated Spirit[1].

Extemporaneous preparation

The following directions apply.

Dissolve the Potassium Hydroxide in 15 mL of Purified Water, add a solution of the Virgin Castor Oil in 63 mL of Ethanol (96 per cent), mix, allow to stand for 1 hour or until a small portion of the mixture remains clear when diluted with 19 times its volume of Purified Water and then add the Oleic Acid. Mix the Terpineol with a solution of the Chloroxylenol in the remainder of the Ethanol (96 per cent), pour into the soap solution and add sufficient Purified Water to produce 1000 mL.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of chloroxylenol, C_8H_9ClO

4.75 to 5.25% w/v.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Ethanol content

16 to 21% v/v, Appendix VIII F.

ASSAY

Dissolve 0.4 g of *4-chloro-o-cresol* (internal standard) in sufficient *chloroform* to produce 50 mL (solution A). Carry out the method for *gas chromatography*, Appendix III B, using solutions prepared in the following manner. For solution (1) dissolve 0.10 g of *chloroxylenol BPCRS* in 10 mL of solution A and dilute to 20 mL with *chloroform*. For solution (2) place 4 mL of the solution being examined in a separating funnel, add 20 mL of *chloroform*, mix, add 4 mL of *2M hydrochloric acid* and shake. Extract with two further 10-mL quantities of *chloroform*. Combine the chloroform extracts, dry by shaking with *anhydrous sodium sulfate* and filter. Prepare solution (3) in the same manner as solution (2) but adding 20 mL of solution A in place of the 20 mL of chloroform.

The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (80 to 100 mesh) coated with 3% w/w of polyethylene glycol (Carbowax 20M is suitable) and maintained at 160°.

Calculate the content of C_8H_9ClO using the declared content of C_8H_9ClO in *chloroxylenol BPCRS*.

1 The law and statutory regulations governing the use of Industrial Methylated Spirit must be observed.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorphenamine Injection

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Chlorphenamine Injection is a sterile solution of Chlorphenamine Maleate in Water for Injections free from dissolved air.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of chlorphenamine maleate, $C_{16}H_{19}ClN_2,C_4H_4O_4$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 20 volumes of 1M *acetic acid*, 30 volumes of *methanol* and 50 volumes of *ethyl acetate* as the mobile phase. Heat the plate at 105° for 30 minutes before use. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) evaporate an appropriate volume to dryness in a current of nitrogen using the minimum amount of heat, dissolve the residue as completely as possible in sufficient *chloroform* to produce a solution containing 0.5% w/v of Chlorphenamine Maleate and centrifuge. Solution (2) contains 0.5% w/v of *chlorphenamine maleate BPCRS* in *chloroform*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The two principal spots in the chromatogram obtained with solution (1) correspond to those in the chromatogram obtained with solution (2). Spray the plate with *dilute potassium iodobismuthate solution*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 5.2, Appendix V L.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of *diethylamine*, 40 volumes of *chloroform* and 50 volumes of *cyclohexane* as the mobile phase but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) evaporate a suitable volume of the injection to dryness in a current of nitrogen using the minimum amount of heat, dissolve the residue as completely as possible in sufficient *chloroform* to produce a solution containing 5% w/v of Chlorphenamine Maleate and centrifuge. For solution (2) dilute 1 volume of solution (1) to 500 volumes with *chloroform*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%). Disregard any spot remaining on the line of application.

ASSAY

Dilute a volume containing 10 mg of Chlorphenamine Maleate to 500 mL with 0.25M *sulfuric acid* and measure the *absorbance* of the resulting solution at the maximum at 265 nm, Appendix II B. Calculate the content of $C_{16}H_{19}ClN_2,C_4H_4O_4$ taking 212 as the value of A(1%, 1 cm) at the maximum at 265 nm.

STORAGE

Chlorphenamine Injection should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

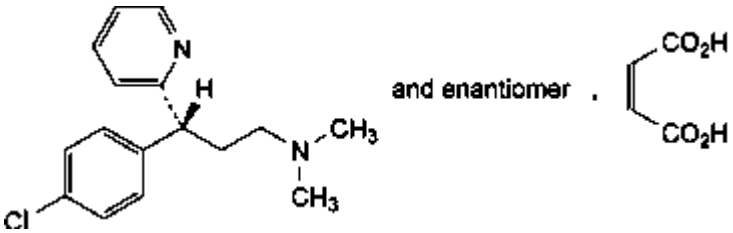
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorphenamine Maleate

General Notices

(Ph. Eur. monograph 0386)



$C_{20}H_{23}ClN_2O_4$ 390.9 *113-92-8*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Preparations

Chlorphenamine Injection

Chlorphenamine Oral Solution

Chlorphenamine Tablets

Ph Eur

DEFINITION

(3*RS*)-3-(4-Chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine hydrogen (*Z*)-butenedioate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 130 °C to 135 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *chlorphenamine maleate CRS*.

C. Optical rotation (see Tests).

TESTS

Solution S

Dissolve 2.0 g in *water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 0.5 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *chlorphenamine impurity C CRS* in 5 mL of the test solution and dilute to 50.0 mL with the mobile phase. Dilute 2 mL of this solution to 20 mL with the mobile phase.

Reference solution (d) Dissolve 5 mg of *2,2'-dipyridylamine R* (impurity B) in the mobile phase and dilute to 100 mL with the mobile phase.

Reference solution (e) Dissolve the contents of a vial of *chlorphenamine impurity A CRS* in 2 mL of the test solution. Sonicate for 5 min.

Column:

— *size*: *l* = 0.30 m, Ø = 3.9 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 20 volumes of *acetonitrile R* and 80 volumes of a 8.57 g/L solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL.

Run time 3.5 times the retention time of chlorphenamine.

Relative retention With reference to chlorphenamine (retention time = about 11 min): maleic acid = about 0.2; impurity A = about 0.3; impurity B = about 0.4; impurity C = about 0.9; impurity D = about 3.0.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity C and chlorphenamine.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.5; impurity B = 1.4;

— *impurity A*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities B, C, D*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to maleic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

www.webofpharma.com

https://thuocngocanh.com/

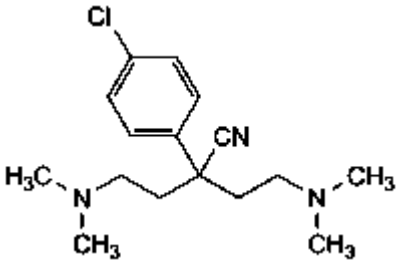
1 mL of *0.1 M perchloric acid* is equivalent to 19.54 mg of $C_{20}H_{23}ClN_2O_4$.

STORAGE

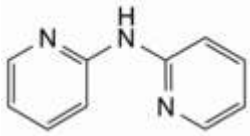
Protected from light.

IMPURITIES

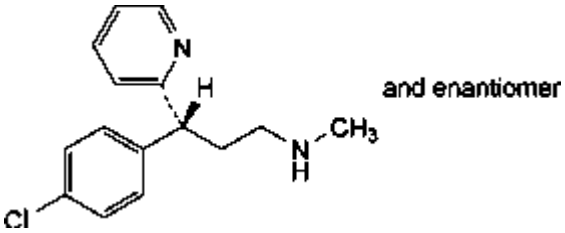
Specified impurities *A, B, C, D.*



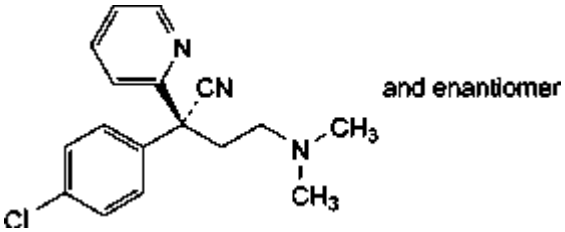
A. 2-(4-chlorophenyl)-4-(dimethylamino)-2-[2-(dimethylamino)ethyl]butanenitrile,



B. *N*-(pyridin-2-yl)pyridin-2-amine (2,2′-dipyridylamine),



C. (3*RS*)-3-(4-chlorophenyl)-*N*-methyl-3-(pyridin-2-yl)propan-1-amine,



D. (2*RS*)-2-(4-chlorophenyl)-4-(dimethylamino)-2-(pyridin-2-yl)butanenitrile.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorphenamine Oral Solution

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Chlorphenamine Oral Solution is a solution of Chlorphenamine Maleate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of chlorphenamine maleate, $C_{16}H_{19}ClN_2,C_4H_4O_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

In the test for Related substances, the principal spot in the chromatogram obtained with solution (3) corresponds to the spot in the chromatogram obtained with solution (4).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the oral solution containing 10 mg of Chlorphenamine Maleate with an equal volume of *water*, add 20 mL of a 10% w/v solution of *sodium hydroxide* and extract with four 15 mL quantities of *chloroform*. Add 1 g of *anhydrous sodium sulfate* to the combined extracts, filter, evaporate at a temperature not exceeding 40° at a pressure of 2 kPa and dissolve the residue in 1 mL of *chloroform*.

(2) Dilute 1 volume of solution (1) to 500 volumes with *chloroform*.

(3) Dilute 1 volume of solution (1) to 10 volumes with *chloroform*.

(4) 0.1% w/v of *chlorphenamine maleate BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

20 volumes of 1M *acetic acid*, 30 volumes of *methanol* and 50 volumes of *ethyl acetate*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *gas chromatography*, Appendix III B.

(1) Add 10 mL of a 10% w/v solution of *sodium hydroxide* in *methanol* and 5 mL of a 0.060% w/v solution of N-*phenylcarbazole* (internal standard) in *chloroform* to a quantity of the oral solution containing 3 mg of Chlorphenamine Maleate, extract with four 25 mL quantities of *chloroform* and wash each extract with the same 10 mL of *water*. Combine the chloroform extracts, shake with *anhydrous sodium sulfate*, filter, evaporate at a temperature not exceeding 40° at a pressure of 2 kPa and dissolve the residue in 2 mL of *chloroform*.

(2) Prepared in the same manner as solution (1), but omitting the internal standard.

(3) 0.15% w/v of *chlorphenamine maleate BPCRS* and 0.15% w/v of N-*phenylcarbazole* (internal standard) in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) (Gas Chrom Q or Diatomite CQ is suitable) coated with 3% w/w of dimethyl silicone fluid (OV-101 is suitable).

(b) Use *nitrogen* as the carrier gas at 50 mL per minute.

(c) Use isothermal conditions maintained at 220°.

(d) Use an inlet temperature of 250°.

(e) Use a flame ionisation detector at a temperature of 300°.

(f) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{19}ClN_2,C_4H_4O_4$ using the declared content of $C_{16}H_{19}ClN_2,C_4H_4O_4$ in *chlorphenamine maleate BPCRS*.

STORAGE

Chlorphenamine Oral Solution should be protected from light.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorphenamine Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Chlorphenamine Tablets contain Chlorphenamine Maleate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of chlorphenamine maleate, $C_{16}H_{19}ClN_2,C_4H_4O_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Comply with the test described under Chlorphenamine Injection using as solution (1) a solution prepared in the following manner. Extract a quantity of the powdered tablets containing 5 mg of Chlorphenamine Maleate with *chloroform*, filter, evaporate to dryness and dissolve the residue in 1 mL of *chloroform*.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of *diethylamine*, 40 volumes of *chloroform* and 50 volumes of *cyclohexane* as the mobile phase but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 50 mg of Chlorphenamine Maleate with *chloroform*, filter, evaporate the filtrate to dryness and dissolve the residue in 1 mL of *chloroform*. For solution (2) dilute 1 volume of solution (1) to 500 volumes with *chloroform*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%). Disregard any spot remaining on the line of application.

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 3 mg of Chlorphenamine Maleate with 20 mL of 0.05M *sulfuric acid* for 5 minutes, add 20 mL of *ether*, shake carefully and filter the acid layer into a second separating funnel. Extract the ether layer with two 10-mL quantities of 0.05M *sulfuric acid*, filter each acid layer into the second separating funnel and wash the filter with 0.05M *sulfuric acid*. Make the combined acid extracts and washings just alkaline to *litmus paper* with 1M *sodium hydroxide*, add 2 mL in excess and extract with two 50 mL quantities of *ether*. Wash each ether extract with the same 20 mL of *water* and extract with successive quantities of

www.webofpharma.com

https://thuocngocanh.com/

20, 20 and 5 mL of 0.25M *sulfuric acid*. Dilute the combined acid extracts to 50 mL with 0.25M *sulfuric acid*, dilute 10 mL to 25 mL with 0.25M *sulfuric acid* and measure the *absorbance* of the resulting solution at the maximum at 265 nm, Appendix II B. Calculate the content of $C_{16}H_{19}ClN_2,C_4H_4O_4$ taking 212 as the value of A(1%, 1 cm) at the maximum at 265 nm.

© Crown Copyright 2022

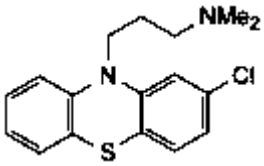
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorpromazine

General Notices



$C_{17}H_{19}ClN_2S$ 318.9 *50-53-3*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Chlorpromazine Suppositories

DEFINITION

Chlorpromazine is [3-(2-chlorophenothiazin-10-yl)propyl]-dimethylamine. It contains not less than 99.0% and not more than 101.0% of $C_{17}H_{19}ClN_2S$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or creamy white powder or waxy solid.

Practically insoluble in *water*; freely soluble in *ethanol (96%)* and in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of chlorpromazine *(RS 056)*.

B. Complies with the test for *identification of phenothiazines*, Appendix III A, using *chlorpromazine hydrochloride BPCRS* to prepare reference solution.

TESTS

Melting point

56° to 58°, Appendix V A.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Complies with the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A*.

Loss on drying

When dried to constant weight over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa, loses not more than 0.5% of its weight.

Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 0.8 g in 300 mL of *acetone* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 3 mL of a saturated solution of *methyl orange* in *acetone* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 31.89 mg of $C_{17}H_{19}ClN_2S$.

STORAGE

Chlorpromazine should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

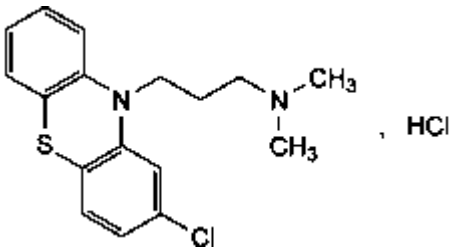
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorpromazine Hydrochloride

General Notices

(Ph. Eur. monograph 0475)



$C_{17}H_{20}Cl_2N_2S$ 355.3 *69-09-0*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparations

Chlorpromazine Injection

Chlorpromazine Oral Solution

Chlorpromazine Tablets

Ph Eur

DEFINITION

3-(2-Chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Very soluble in water, freely soluble in ethanol (96 per cent).

It decomposes on exposure to air and light.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation 60 g/L solutions in *methylene chloride R*.

Comparison *chlorpromazine hydrochloride CRS*.

B. Identification of phenothiazines by thin-layer chromatography (*2.3.3*): use *chlorpromazine hydrochloride CRS* to prepare the reference solution.

C. Dissolve 20 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

pH (*2.2.3*)

3.5 to 4.5. *Carry out the test protected from light and use freshly prepared solutions.*

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Impurity F

Thin-layer chromatography (*2.2.27*). *Prepare the solutions immediately before use and protect from light*.

Solvent mixture *diethylamine R*, *methanol R* (5:95 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *chlorpromazine impurity F CRS* in 2.0 mL of the solvent mixture.

Reference solution (b) Dilute 300 µL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 0.10 g of the substance to be examined in the solvent mixture, add 1 mL of reference solution (a) and dilute to 5 mL with the solvent mixture.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *acetone R*, *diethylamine R*, *cyclohexane R* (10:10:80 *V/V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Application 10 µL of the test solution and reference solutions (b) and (c).

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Impurity F = about 0.5; chlorpromazine = about 0.6.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated spots due to impurity F and chlorpromazine.

Limit:

— *impurity F*: any spot due to impurity F is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.15 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 4 mg of *chlorpromazine impurity D CRS* in the mobile phase and dilute to 10 mL with the mobile phase. To 1 mL of the solution add 1 mL of the test solution and dilute to 100 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 4.0 mg of *chlorpromazine impurity A CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve 4 mg of *promazine hydrochloride CRS* (impurity C) and 4.0 mg of *chlorpromazine impurity E CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 0.2 volumes of *thiodiethylene glycol R*, 50 volumes of *acetonitrile R* and 50 volumes of a 0.5 per cent *V/V* solution of *trifluoroacetic acid R* previously adjusted to pH 5.3 with *tetramethylethylenediamine R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 10 µL.

Run time 4 times the retention time of chlorpromazine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities C and E; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to chlorpromazine (retention time = about 8 min): impurity A = about 0.4; impurity B = about 0.5; impurity C = about 0.7; impurity D = about 0.9; impurity E = about 3.4.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity D and chlorpromazine.

Limits:

— *impurities B, C, D*: for each impurity, not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *impurity E*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: maximum 1.0 per cent;

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.1 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 35.53 mg of $C_{17}H_{20}Cl_2N_2S$.

www.webofpharma.com

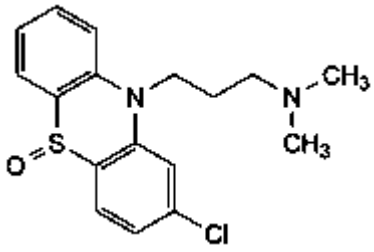
https://thuocngocanh.com/

STORAGE

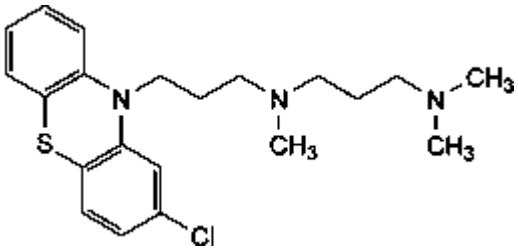
In an airtight container, protected from light.

IMPURITIES

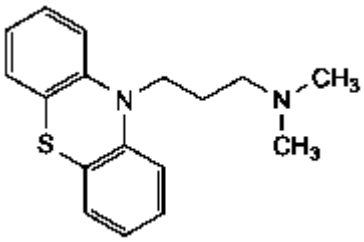
Specified impurities *A, B, C, D, E, F.*



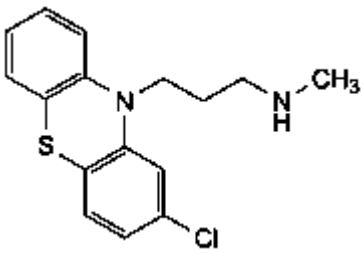
A. 2-chloro-10-[3-(dimethylamino)propyl]-5λ^4-phenothiazin-5(10*H*)-one (chlorpromazine sulfoxide),



B. *N*^{1}-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-*N*^{1},*N*^{3},*N*^{3}-trimethylpropane-1,3-diamine,



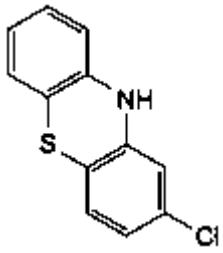
C. *N*,*N*-dimethyl-3-(10*H*-phenothiazin-10-yl)propan-1-amine (promazine),



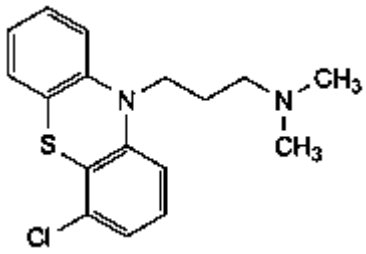
D. 3-(2-chloro-10*H*-phenothiazin-10-yl)-*N*-methylpropan-1-amine (demethylchlorpromazine),

www.webofpharma.com

https://thuocngocanh.com/



E. 2-chloro-10*H*-phenothiazine,



F. 3-(4-chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorpromazine Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Chlorpromazine Injection is a sterile solution of Chlorpromazine Hydrochloride in Water for Injections free from dissolved air.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of chlorpromazine hydrochloride, $C_{17}H_{19}ClN_2S,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. To a volume containing 0.1 g of Chlorpromazine Hydrochloride add 20 mL of *water* and 2 mL of 10M *sodium hydroxide*. Shake and extract with 25 mL of *ether*. Wash the ether layer with two 5 mL quantities of *water*, dry with *anhydrous sodium sulfate*, evaporate the ether and dissolve the residue in 1 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of chlorpromazine *(RS 056)*.

B. Complies with the test for *identification of phenothiazines*, Appendix III A. For solution (1) dilute the injection with *water* to give a solution containing 0.2% w/v of Chlorpromazine Hydrochloride.

TESTS

Acidity

pH, 5.0 to 6.5, Appendix V L.

Related substances

Carry out the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A* and applying separately to the plate 20 µL of each of the following freshly prepared solutions. For solution (1) dilute a volume of the injection, if necessary, with sufficient of a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine* to produce a solution containing 0.5% w/v of Chlorpromazine Hydrochloride. For solution (2) dilute 1 volume of solution (1) to 20 volumes with the same solvent. For solution (3) dilute 1 volume of solution (1) to 200

www.webofpharma.com

https://thuocngocanh.com/

volumes with the same solvent. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3).

ASSAY

Carry out the following procedure protected from light. Dilute a suitable volume with sufficient 0.1M *hydrochloric acid* to produce a solution containing 0.0005% w/v of Chlorpromazine Hydrochloride and measure the *absorbance* at the maximum at 254 nm, Appendix II B. Calculate the content of $C_{17}H_{19}ClN_2S,HCl$ taking 915 as the value of A(1%, 1 cm) at the maximum at 254 nm.

STORAGE

Chlorpromazine Injection should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorpromazine Oral Solution

General Notices

Chlorpromazine Elixir

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Chlorpromazine Oral Solution is a solution of Chlorpromazine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of chlorpromazine hydrochloride, $C_{17}H_{19}ClN_2S,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Carry out the method for *identification of phenothiazines*, Appendix III A. For solution (1) dilute a suitable volume of the oral solution with *water* to give a solution containing 0.2% w/v of Chlorpromazine Hydrochloride.

TESTS

Related substances

Carry out the procedure protected from light under an atmosphere of nitrogen. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 40 mL of *water* and 5 mL of a 20% w/v solution of *sodium hydroxide* to a quantity of the oral solution containing 20 mg of Chlorpromazine Hydrochloride in a separating funnel and swirl to mix. Extract with two 25-mL quantities of *chloroform*, combine the chloroform extracts and filter through *anhydrous sodium sulfate*. Wash the sodium sulfate with a further 25 mL of *chloroform* and evaporate the combined filtrate and washings to dryness at about 30° in a gentle current of *nitrogen*. Dissolve the residue in 2 mL of a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*.

(2) Dilute 1 volume of solution (1) to 200 volumes with a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*.

(3) 0.030% w/v solution of *chlorpromazine sulfoxide BPCRS* in a mixture of 5 volumes of *diethylamine* and 95 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254}.

(b) Use the mobile phase as described below. Use an atmosphere of nitrogen.

www.webofpharma.com

https://thuocngocanh.com/

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry in air, spray with 20% w/w solution of *perchloric acid* and heat at 100° for 5 minutes.

MOBILE PHASE

10 volumes of *acetone*, 10 volumes of *diethylamine* and 80 volumes of *cyclohexane*.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to chlorpromazine sulfoxide is not more intense than the spot in the chromatogram obtained with solution (3);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2).

Disregard any spot remaining on the line of application.

ASSAY

Carry out the following procedure protected from light. Dilute a quantity containing 0.1 g of Chlorpromazine Hydrochloride to 500 mL with 2 M *hydrochloric acid*. To 10 mL of this solution add 20 mL of *water*, make distinctly alkaline to *litmus paper* with 13.5M *ammonia* and extract with six 25 mL quantities of *ether*. Extract the combined ether solutions with four 25 mL quantities of a mixture containing 1 volume of *hydrochloric acid* and 99 volumes of *water*, discard the ether, remove any dissolved ether from the combined extracts with a current of air and dilute to 250 mL with a mixture containing 1 volume of *hydrochloric acid* and 99 volumes of *water*. Measure the *absorbance* of the resulting solution at the maximum at 254 nm, Appendix II B. Calculate the content of $C_{17}H_{19}ClN_2S,HCl$ taking 914 as the value of A(1%, 1 cm) at the maximum at 254 nm.

STORAGE

Chlorpromazine Oral Solution should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorpromazine Suppositories

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Chlorpromazine Suppositories contain Chlorpromazine in a suitable suppository basis.

The suppositories comply with the requirements stated under Rectal Preparations and with the following requirements.

Content of chlorpromazine, $C_{17}H_{19}ClN_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Comply with the test for *identification of phenothiazines*, Appendix III A. For solution (1) dissolve a quantity of the suppositories containing 0.1 g of Chlorpromazine in 50 mL of *chloroform*. Use *chlorpromazine hydrochloride BPCRS* to prepare solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, protected from light using the following solutions.

(1) Dissolve a quantity of the suppositories containing 0.2 g of Chlorpromazine in sufficient *chloroform* to produce 20 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes with *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *acetone*, 10 volumes of *diethylamine* and 80 volumes of *cyclohexane*.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

Disregard any spot remaining on the line of application.

ASSAY

Weigh five suppositories. Dissolve a quantity containing 0.5 g of Chlorpromazine in sufficient *chloroform* to produce 100 mL and dilute 20 mL to 100 mL with *ethanol (96%)*. Dilute 10 mL of this solution to 100 mL with *ethanol (96%)* and further dilute 5 mL of this solution to 100 mL with the same solvent. Measure the *absorbance* of the resulting solution at the maximum at 258 nm, Appendix II B, using *ethanol (96%)* in the reference cell. Calculate the content of $C_{17}H_{19}ClN_2S$ taking 1150 as the value of A(1%, 1 cm) at the maximum at 258 nm.

STORAGE

Chlorpromazine Suppositories should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorpromazine Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Chlorpromazine Tablets contain Chlorpromazine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of chlorpromazine hydrochloride, $C_{17}H_{19}ClN_2S,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 40 mg of Chlorpromazine Hydrochloride add 10 mL of *water* and 2 mL of 10M *sodium hydroxide*. Shake and extract with 15 mL of *ether*. Wash the ether layer with two 5-mL quantities of *water*, dry with *anhydrous sodium sulfate* and evaporate the ether. Dissolve the residue in 0.4 mL of *chloroform*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of chlorpromazine *(RS 056)*.

B. Comply with the test for *identification of phenothiazines*, Appendix III A. For solution (1) shake a quantity of the powdered tablets with sufficient *chloroform* to produce a solution containing 0.20% w/v of Chlorpromazine Hydrochloride, centrifuge and use the supernatant liquid.

TESTS

Related substances

Comply with the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A* and the following freshly prepared solutions. For solution (1) extract a quantity of the powdered tablets containing 0.1 g of Chlorpromazine Hydrochloride with 10 mL of a mixture of 95 volumes of *methanol* and 5 volumes of *diethylamine* and filter. For solution (2) dilute 1 volume of solution (1) to 200 volumes with the same solvent mixture.

Dissolution

Carry out the procedure protected from light. Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium to produce a solution containing 0.0005% % w/v of Chlorpromazine Hydrochloride, at the maximum at 254 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}ClN_2S,HCl$, in the medium taking 914 as the value of A(1%, 1 cm) at the maximum at 254 nm.

ASSAY

Carry out the following procedure protected from light. Powder 10 tablets without loss, triturate the powder with 10 mL of *absolute ethanol*, add about 300 mL of 0.1M *hydrochloric acid* and shake for 15 minutes. Add sufficient 0.1M *hydrochloric acid* to produce 500 mL, filter, dilute a volume of the filtrate containing 5 mg of Chlorpromazine Hydrochloride to 100 mL with 0.1M *hydrochloric acid* and further dilute 10 mL to 100 mL with the same solvent. Measure the *absorbance* of the resulting solution at the maximum at 254 nm, Appendix II B. Calculate the content of $C_{17}H_{19}ClN_2S,HCl$ taking 915 as the value of A(1%, 1 cm) at the maximum at 254 nm.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

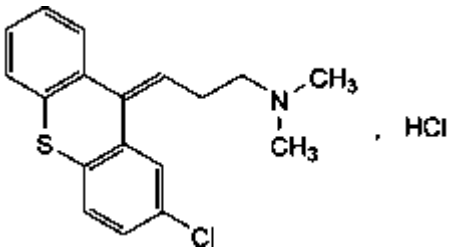
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlorprothixene Hydrochloride

General Notices

(Ph. Eur. monograph 0815)



$C_{18}H_{19}Cl_2NS$ 352.3 *6469-93-8*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

(3*Z*)-3-(2-Chloro-9*H*-thioxanthen-9-ylidene)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water and in ethanol (96 per cent), slightly soluble in methylene chloride.

mp

About 220 °C.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, E.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 25 mg in 1 mL of water R, add 0.1 mL of dilute sodium hydroxide solution R and shake with 2 mL of methylene chloride R; separate the organic layer and wash with 0.5 mL of water R; evaporate the organic layer to dryness and dry the residue at 40-50 °C; examine the residue as a disc.

Comparison Repeat the operations using 25 mg of chlorprothixene hydrochloride CRS.

B. Dissolve 0.2 g in a mixture of 5 mL of dioxan R and 5 mL of a 1.5 g/L solution of sodium nitrite R. Add 0.8 mL of nitric acid R. After 10 min, add the solution to 20 mL of water R. Filter the precipate formed after 1 h. The filtrate is used immediately for identification test C. Dissolve the precipitate by warming in about 15 mL of ethanol (96 per cent) R and add the solution to 10 mL of water R. Filter and dry the precipitate at 100-105 °C for 2 h. The melting point (2.2.14) is 152 °C to 154 °C.

C. To 1 mL of the filtrate obtained in identification test B, add 0.2 mL of a suspension of 50 mg of fast red B salt R in 1 mL of ethanol (96 per cent) R. Add 1 mL of 0.5 M alcoholic potassium hydroxide. A dark red colour is produced. Carry out a blank test.

D. Dissolve about 20 mg in 2 mL of nitric acid R. A red colour is produced. Add 5 mL of water R and examine in ultraviolet light at 365 nm. The solution shows green fluorescence.

E. Dissolve 20 mg in 2 mL of water R, acidify with dilute nitric acid R and allow to stand for 5 min. Centrifuge. The supernatant gives reaction (a) of chlorides (2.3.1) starting from ‘add 0.4 mL of silver nitrate solution R1'.

TESTS

Solution S

Dissolve 0.25 g in carbon dioxide-free water R and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

pH (2.2.3)

4.4 to 5.2 for solution S.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from bright light.*

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve the contents of a vial of *chlorprothixene for system suitability CRS* (containing impurities C and F) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Solution containing 6.0 g/L of *potassium dihydrogen phosphate R*, 2.9 g/L of *sodium laurilsulfate R* and 9 g/L of *tetrabutylammonium bromide R* in a mixture of 50 volumes of *methanol R*, 400 volumes of *acetonitrile R* and 550 volumes of *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Equilibration For about 30 min with the mobile phase.

Injection 20 µL.

Run time Twice the retention time of chlorprothixene.

Identification of impurities Use the chromatogram supplied with *chlorprothixene for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C and F.

Relative retention With reference to chlorprothixene (retention time = about 10 min): impurity C = about 1.25; impurity F = about 1.33.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to chlorprothixene and impurity C.

Limits:

— *impurity F*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (*2.4.14*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 35.23 mg of $C_{18}H_{19}Cl_2NS$.

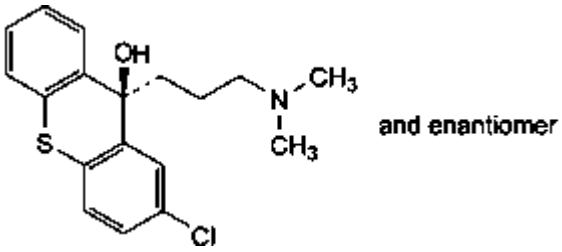
STORAGE

Protected from light.

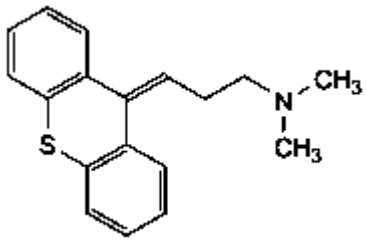
IMPURITIES

Specified impurities F.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E.



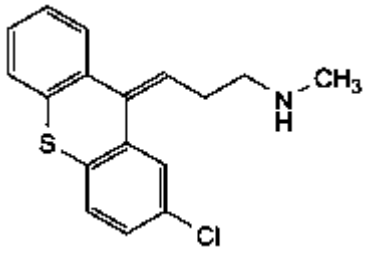
A. (3*RS*)-2-chloro-9-[3-(dimethylamino)propyl]-9*H*-thioxanthen-9-ol,



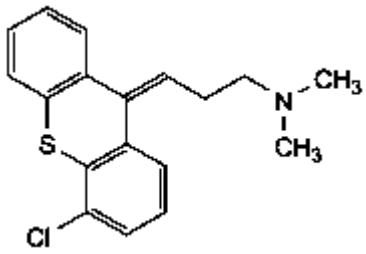
B. *N,N*-dimethyl-3-(9*H*-thioxanthen-9-ylidene)propan-1-amine,

www.webofpharma.com

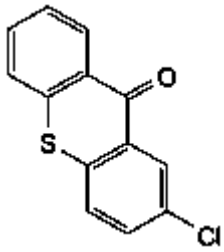
https://thuocngocanh.com/



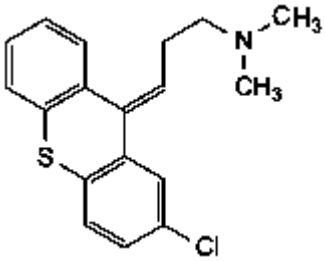
C. (3*Z*)-3-(2-chloro-9*H*-thioxanthen-9-ylidene)-*N*-methylpropan-1-amine,



D. (3*Z*)-3-(4-chloro-9*H*-thioxanthen-9-ylidene)-*N,N*-dimethylpropan-1-amine,



E. 2-chloro-9*H*-thioxanthen-9-one,



F. (3*E*)-3-(2-chloro-9*H*-thioxanthen-9-ylidene)-*N,N*-dimethylpropan-1-amine ((*E*)-chlorprothixene).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

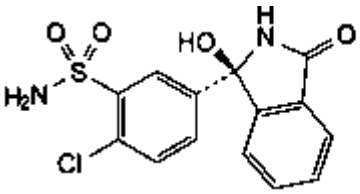
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlortalidone

General Notices

(Ph. Eur. monograph 0546)



and enantiomer

$C_{14}H_{11}ClN_2O_4S$ 338.8 *77-36-1*

Action and use

Thiazide-like diuretic.

Preparations

Chlortalidone Tablets

Co-tenidone Tablets

Ph Eur

DEFINITION

2-Chloro-5-[(1*RS*)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]benzene-1-sulfonamide.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Very slightly soluble in water, soluble in acetone and in methanol, practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison chlortalidone CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Acidity

Dissolve 1.0 g with heating in a mixture of 25 mL of acetone R and 25 mL of carbon dioxide-free water R. Cool. Titrate with 0.1 M sodium hydroxide, determining the end-point potentiometrically (2.2.20). Not more than 0.75 mL of 0.1 M sodium hydroxide is required.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mix 2 volumes of a 2 g/L solution of sodium hydroxide R, 48 volumes of mobile phase B and 50 volumes of mobile phase A.

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of chlortalidone for system suitability CRS (containing impurities B and G) in 1 mL of the solvent mixture. Dilute 400 µL of the solution to 2 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of chlortalidone CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: dissolve 1.32 g of *ammonium phosphate R* in about 900 mL of *water for chromatography R* and adjust to pH 5.5 with *dilute phosphoric acid R*; dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *methanol R2*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 16	65	35
16 - 21	65 → 50	35 → 50
21 - 45	50	50

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *chlortalidone for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and G.

Relative retention With reference to chlortalidone (retention time = about 7 min): impurity B = about 0.7; impurity G = about 5.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity B and chlortalidone.

Limits:

— *impurity B*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *impurity G*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 12 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (*2.4.4*)

Maximum 350 ppm.

www.webofpharma.com

https://thuocngocanh.com/

Triturate 0.3 g finely, add 30 mL of *water R*, shake for 5 min and filter. 15 mL of the filtrate complies with the test. Prepare the standard using 10 mL of *chloride standard solution (5 ppm Cl) R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

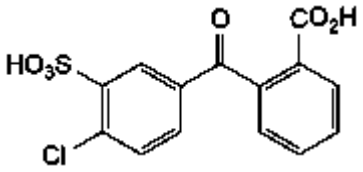
Injection 20 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_{14}H_{11}ClN_2O_4S$ taking into account the assigned content of *chlortalidone CRS*.

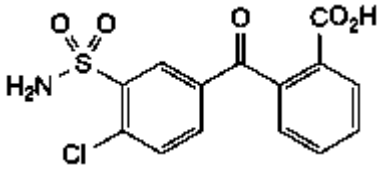
IMPURITIES

Specified impurities *B, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, F, H, I.*



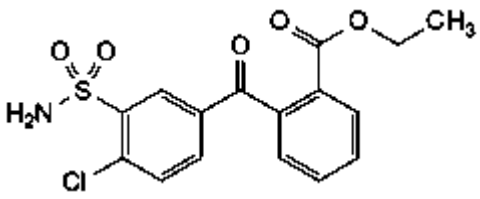
A. 2-(4-chloro-3-sulfobenzoyl)benzoic acid,



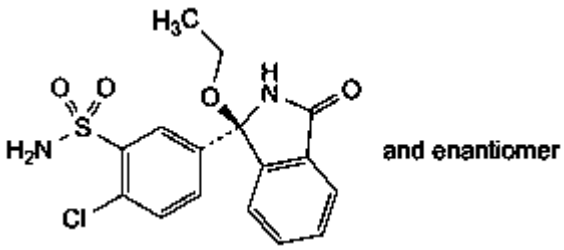
B. 2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid,

www.webofpharma.com

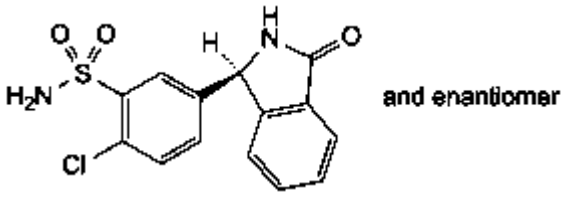
https://thuocngocanh.com/



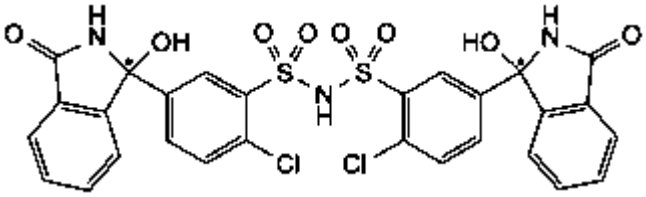
C. ethyl 2-(4-chloro-3-sulfamoylbenzoyl)benzoate,



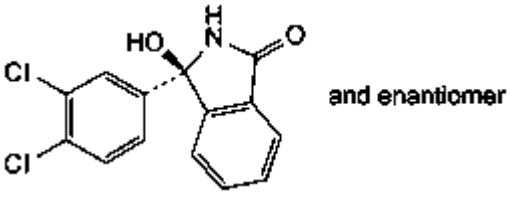
D. 2-chloro-5-[(1*RS*)-1-ethoxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]benzene-1-sulfonamide,



E. 2-chloro-5-[(1*RS*)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]benzene-1-sulfonamide,



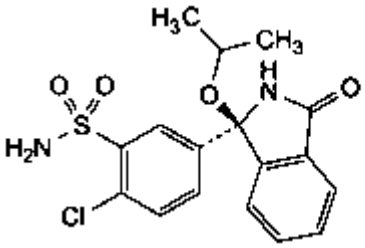
F. (1$^{1}\Xi$,7$^{1}\Xi$)-2^{4},6^{6}-dichloro-1^{1},7^{1}-dihydroxy-1^{2},1^{3},7^{2},7^{3}-tetrahydro-1^{1}*H*,7^{1}*H*-3λ^{6},5λ^{6}-dithia-4-aza-1,7(1)-diisoindola-2,6(1,3)-dibenzaheptaphan-1^{3},3,3,5,5,7^{3}-hexone,



G. (3*RS*)-3-(3,4-dichlorophenyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one,

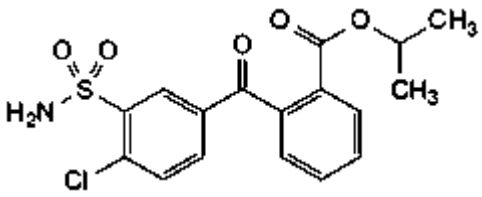
www.webofpharma.com

https://thuocngocanh.com/



and enantiomer

H. 2-chloro-5-[(1*RS*)-3-oxo-1-[(propan-2-yl)oxy]-2,3-dihydro-1*H*-isoindol-1-yl]benzene-1-sulfonamide,



I. propan-2-yl 2-(4-chloro-3-sulfamoylbenzoyl)benzoate.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlortalidone Tablets

General Notices

Action and use

Thiazide-like diuretic.

DEFINITION

Chlortalidone Tablets contain Chlortalidone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of chlortalidone, $C_{14}H_{11}ClN_2O_4S$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Heat a quantity of the powdered tablets containing 0.2 g of Chlortalidone with 20 mL of *acetone* on a water bath for 10 minutes, cool and filter. Add 40 mL of *water* to the filtrate and heat on a water bath for 20 minutes using a gentle current of air to remove the acetone. Cool the solution to room temperature, allow to stand, filter and dry the crystals at 105° for 4 hours. The *infrared spectrum* of the crystals, Appendix II A, is concordant with the *reference spectrum* of chlortalidone *(RS 058)*.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 5 volumes of *toluene*, 10 volumes of *xylene*, 20 volumes of 18M *ammonia*, 30 volumes of *1,4-dioxan* and 30 volumes of *propan-2-ol* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) add a quantity of the powdered tablets containing 0.1 g of Chlortalidone to 5 mL of *ethanol (96%)*, mix with the aid of ultrasound for 15 minutes, centrifuge and use the supernatant liquid. For solution (2) dilute 1 volume of solution (1) to 200 volumes with *ethanol (96%)*. Solution (3) contains 0.020% w/v of *2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid BPCRS* in *ethanol (96%)*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Any spot corresponding to 2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (1%) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. Boil a quantity of the powder containing 0.1 g of Chlortalidone under a reflux condenser with 30 mL of *methanol* for 5 minutes, shake vigorously for 15 minutes, cool and filter. Wash the residue and filter with *methanol* and dilute the combined filtrate and washings to 100 mL with *methanol*. To 5 mL add 2 mL of 1M *hydrochloric acid* and sufficient *methanol* to produce 50 mL and

www.webofpharma.com

https://thuocngocanh.com/

measure the *absorbance* of the resulting solution at the maximum at 275 nm, Appendix II B. Calculate the content of $C_{14}H_{11}ClN_2O_4S$ taking 57.4 as the value of A(1%, 1 cm) at the maximum at 275 nm.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlortetracycline Eye Ointment

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Chlortetracycline Eye Ointment is a sterile preparation containing Chlortetracycline Hydrochloride in a suitable basis.

The eye ointment complies with the requirements stated under Eye Preparations and with the following requirements.

Content of chlortetracycline hydrochloride, $C_{22}H_{23}ClN_2O_8,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Disperse a quantity of the eye ointment containing 10 mg of Chlortetracycline Hydrochloride in 10 mL of *dichloromethane*, extract with two 10-mL quantities of 0.01M *hydrochloric acid*, filter and dilute the filtrate to 100 mL with 0.01M *hydrochloric acid*. Dilute 20 mL of the resulting solution to 100 mL with 0.01M *hydrochloric acid*. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 420 nm exhibits two maxima, at 266 nm and 368 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the eye ointment containing 25 mg of Chlortetracycline Hydrochloride in 25 mL of *dichloromethane*, extract with two 10 mL quantities of 0.01M *hydrochloric acid*, filter the aqueous layer and dilute to 50 mL with *water*.

(2) 0.05% w/v of *chlortetracycline hydrochloride BPCRS* in *methanol*.

(3) 0.05% w/v of each of *chlortetracycline hydrochloride BPCRS*, *tetracycline hydrochloride BPCRS* and *metacycline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use *silica gel H* as the coating substance. Adjust the pH of a 10% w/v solution of *disodium edetate* to 8.0 with 10M *sodium hydroxide* and spray the solution evenly onto the plate (about 10 mL for a plate 100 mm × 200 mm). Allow the plate to dry in a horizontal position for at least 1 hour. At the time of use, dry the plate in an oven at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in a current of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. To a quantity of the eye ointment containing 0.5 mg of Chlortetracycline Hydrochloride add 2 mL of *sulfuric acid*; a deep blue colour is produced, which becomes bluish green. Add 1 mL of *water*; a brown colour is produced.

TESTS

Tetracycline hydrochloride and 4-epichlortetracycline hydrochloride

Not more than 8.0% and 6.0% respectively, determined as described under Assay. Inject separately solutions (1) and (4).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, *prepared immediately before use*.

(1) Disperse a quantity of the eye ointment containing 25 mg of Chlortetracycline Hydrochloride in 20 mL of *chloroform* and 50 mL of 0.01 M *hydrochloric acid* and shake for 15 minutes. Dilute to 100 mL with 0.01M *hydrochloric acid*, mix thoroughly, allow to separate and filter the aqueous layer.

(2) Dissolve 25 mg of *chlortetracycline hydrochloride BPCRS* in 20 mL of *chloroform* and 50 mL of 0.01M *hydrochloric acid* and shake for 15 minutes. Dilute to 100 mL with 0.01M *hydrochloric acid*, mix thoroughly, allow to separate and filter the aqueous layer.

(3) 0.025% w/v of each of *chlortetracycline hydrochloride BPCRS* and *4-epichlortetracycline hydrochloride* in 0.01M *hydrochloric acid*.

(4) 0.002% w/v of *tetracycline hydrochloride BPCRS* and 0.0015% w/v of *4-epichlortetracycline hydrochloride* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 355 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *dimethylformamide* and 80 volumes of 0.1M *oxalic acid* the pH of which has been adjusted to 2.2 with *triethylamine*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 1.5.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{22}H_{23}ClN_2O_8$,HCl in the eye ointment using the declared content of $C_{22}H_{23}ClN_2O_8$,HCl in *chlortetracycline hydrochloride BPCRS*.

STORAGE

Chlortetracycline Eye Ointment should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

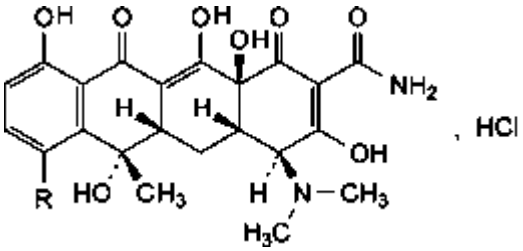
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlortetracycline Hydrochloride

General Notices

(Ph. Eur. monograph 0173)



Compound	R	Molecular formula	M_r
Chlortetracycline hydrochloride	Cl	$C_{22}H_{24}Cl_2N_2O_8$	515.3
Tetracycline hydrochloride	H	$C_{22}H_{25}ClN_2O_8$	480.9

Chlortetracycline hydrochloride *64-72-2*

Tetracycline hydrochloride *64-75-5*

Action and use

Tetracycline antibacterial.

Ph Eur

DEFINITION

Mixture of antibiotics, the main component being the hydrochloride of (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (chlortetracycline hydrochloride), a substance produced by the growth of certain strains of *Streptomyces aureofaciens* or obtained by any other means.

Content

— *chlortetracycline hydrochloride* ($C_{22}H_{24}Cl_2N_2O_8$): minimum 89.5 per cent (anhydrous substance);

— *tetracycline hydrochloride* ($C_{22}H_{25}ClN_2O_8$): maximum 6.0 per cent (anhydrous substance);

— *sum of the contents of chlortetracycline hydrochloride and tetracycline hydrochloride*: 94.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

CHARACTERS

Appearance

Yellow powder.

Solubility

Slightly soluble in water and in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: C, D.

Second identification: A, B, C.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *chlortetracycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *chlortetracycline hydrochloride CRS*, 5 mg of *demeclocycline hydrochloride R* and 5 mg of *doxycycline R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase Mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a 63 g/L solution of *oxalic acid R* previously adjusted to pH 2 with *concentrated ammonia R*.

Application 1 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

B. To about 2 mg add 5 mL of *sulfuric acid R*. A deep blue colour develops and becomes bluish-green. Add the solution to 2.5 mL of *water R*. The colour becomes brownish.

C. It gives reaction (a) of chlorides (2.3.1).

D. Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

pH (2.2.3)

2.3 to 3.3.

Dissolve 0.1 g in 10 mL of *carbon dioxide-free water R*, heating slightly.

Specific optical rotation (2.2.7)

-250 to -235 (anhydrous substance).

Dissolve 0.125 g in *water R* and dilute to 50.0 mL with the same solvent.

Absorbance (2.2.25)

Maximum 0.40 at 460 nm.

Dissolve 0.125 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 25.0 mg of the substance to be examined in mobile phase B and dilute to 25.0 mL with mobile phase B.

Reference solution (a) Dissolve 25.0 mg of *chlortetracycline hydrochloride CRS* in mobile phase B and dilute to 25.0 mL with mobile phase B.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase B.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with mobile phase B.

Reference solution (d) Dissolve 5 mg of *chlortetracycline for system suitability CRS* (containing impurities A, B, D, E, G, H, J, K and L) in mobile phase B and dilute to 5 mL with mobile phase B.

Reference solution (e) Dissolve 25.0 mg of *tetracycline hydrochloride CRS* in mobile phase B and dilute to 25.0 mL with mobile phase B. Dilute 5.0 mL of this solution to 100.0 mL with mobile phase B.

Column:

— *size*: *l* = 0.075 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography with embedded polar groups R* (3.5 µm);

— *temperature*: 45 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: to 725 mL of *water for chromatography R* add 50 mL of *perchloric acid solution R*, shake and add 225 mL of *dimethyl sulfoxide R*;

— *mobile phase B*: to 250 mL of *water for chromatography R* add 50 mL of *perchloric acid solution R*, shake and add 700 mL of *dimethyl sulfoxide R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 46	100 → 0	0 → 100

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *chlortetracycline for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, D, E, G, H, J, K and L.

Relative retention With reference to chlortetracycline (retention time = about 26 min): impurity D = about 0.5; tetracycline = about 0.6; impurity E = about 0.7; impurity B = about 0.8, impurity A = about 0.86; impurity G = about 0.9; impurity H = about 1.1; impurity J = about 1.4, impurity K = about 1.67; impurity L = about 1.71.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to tetracycline and impurity E; minimum 1.5 between the peaks due to impurities A and G; minimum 1.5 between the peaks due to impurities K and L; if necessary, adjust the concentration of dimethyl sulfoxide in mobile phase A.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity G = 1.4; impurity J = 0.3; impurity K = 0.4; impurity L = 0.4;

— *impurity A*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (4.0 per cent);

— *impurities B, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity J*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *impurities D, G, H, L*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity K*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *sum of impurities other than A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (2.5.12)

Maximum 2.0 per cent, determined on 0.300 g.

Sulfated ash (2.4.14)

Maximum 0.5 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

Less than 1 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 10 µL of the test solution and reference solutions (a) and (e).

Calculate the percentage content of $C_{22}H_{24}Cl_2N_2O_8$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *chlortetracycline hydrochloride CRS*. Calculate the percentage content of $C_{22}H_{25}ClN_2O_8$ using the chromatogram obtained with reference solution (e) and taking into account the assigned content of *tetracycline hydrochloride CRS*.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

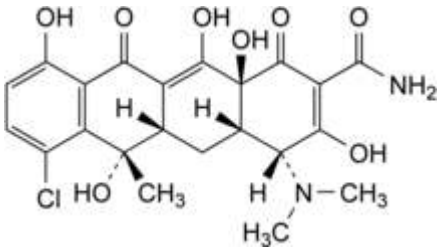
Specified impurities *A, B, D, E, G, H, J, K, L.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

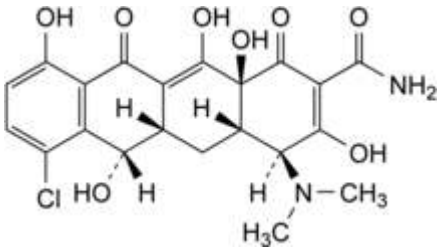
www.webofpharma.com

https://thuocngocanh.com/

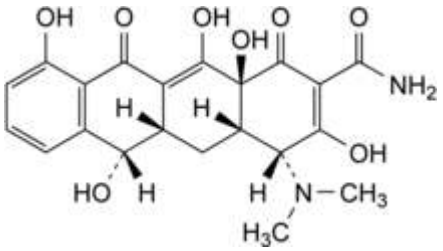
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, F, I.



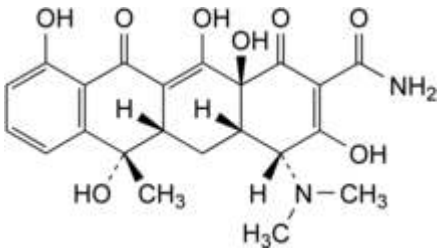
A. (4*R*,4a*S*,5a*S*,6*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epichlortetracycline),



B. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (demeclocycline),



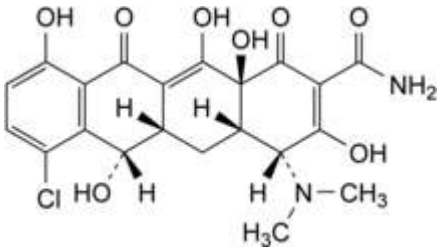
C. (4*R*,4a*S*,5a*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epidemethyltetracycline),



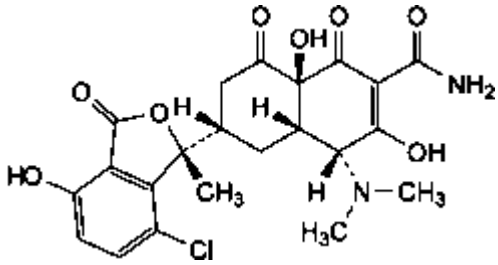
D. (4*R*,4a*S*,5a*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epitetracycline),

www.webofpharma.com

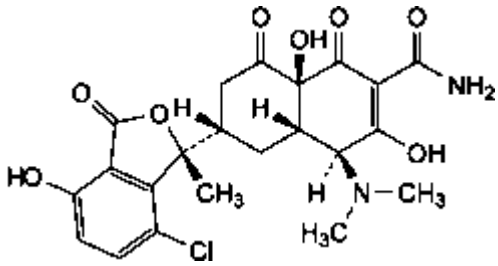
https://thuocngocanh.com/



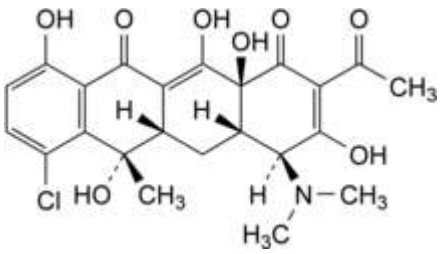
E. (4*R*,4a*S*,5a*S*,6*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epidemethylchlortetracycline),



F. (4*R*,4a*S*,6*S*,8a*S*)-6-[(1*R*)-7-chloro-4-hydroxy-1-methyl-3-oxo-1,3-dihydro-2-benzofuran-1-yl]-4-(dimethylamino)-3,8a-dihydroxy-1,8-dioxo-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxamide (4-epiisochlortetracycline),



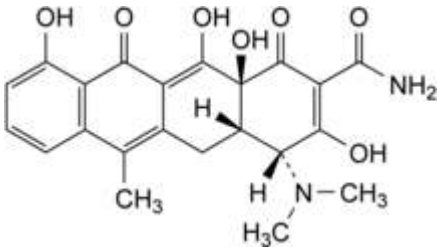
G. (4*S*,4a*S*,6*S*,8a*S*)-6-[(1*R*)-7-chloro-4-hydroxy-1-methyl-3-oxo-1,3-dihydro-2-benzofuran-1-yl]-4-(dimethylamino)-3,8a-dihydroxy-1,8-dioxo-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxamide (isochlortetracycline),



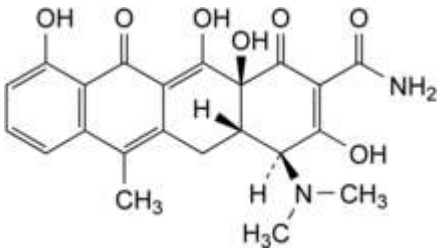
H. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-2-acetyl-7-chloro-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione (2-acetyl-2-decarboxamidochlortetracycline),

www.webofpharma.com

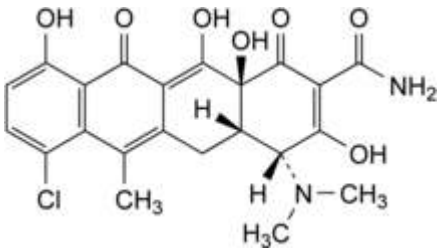
https://thuocngocanh.com/



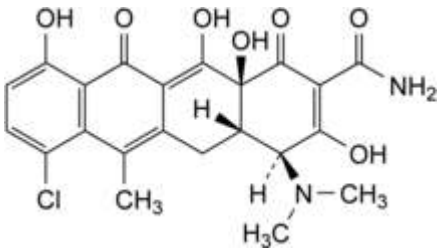
I. (4*R*,4a*S*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,11,12a-hexahydrotetracene-2-carboxamide (4-epianhydrotetracycline),



J. (4*S*,4a*S*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,11,12a-hexahydrotetracene-2-carboxamide (anhydrotetracycline),



K. (4*R*,4a*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,11,12a-hexahydrotetracene-2-carboxamide (4-epianhydrochlortetracycline),



L. (4*S*,4a*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,11,12a-hexahydrotetracene-2-carboxamide (anhydrochlortetracycline).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Chlortetracycline Ointment

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Chlortetracycline Ointment contains Chlortetracycline Hydrochloride in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of chlortetracycline hydrochloride, $C_{22}H_{23}ClN_2O_8,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Disperse a quantity of the ointment containing 10 mg of Chlortetracycline Hydrochloride in 10 mL of *dichloromethane*, extract with two 10-mL quantities of 0.01M *hydrochloric acid*, combine the aqueous extracts, filter and extract the filtrate with two 10-mL quantities of *ether*. Discard the ether extracts and dilute the aqueous layer to 100 mL with 0.01M *hydrochloric acid*. Dilute 20 mL of the resulting solution to 100 mL with 0.01M *hydrochloric acid*. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 420 nm exhibits two maxima, at 266 nm and 368 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the ointment containing 25 mg of Chlortetracycline Hydrochloride in 25 mL of *dichloromethane*, extract with two 10 mL quantities of 0.01M *hydrochloric acid*, filter the aqueous layer and dilute to 50 mL with *water*.

(2) 0.05% w/v of *chlortetracycline hydrochloride BPCRS* in *methanol*.

(3) 0.05% w/v of each of *chlortetracycline hydrochloride BPCRS*, *tetracycline hydrochloride BPCRS* and *metacycline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use *silica gel H* as the coating. Adjust the pH of a 10% w/v solution of *disodium edetate* to 8.0 with 10M *sodium hydroxide* and spray the solution evenly onto the plate (about 10 mL for a plate 100 mm × 200 mm). Allow the plate to dry in a horizontal position for at least 1 hour. At the time of use, dry the plate in an oven at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in a current of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

C. To a quantity of the ointment containing 0.5 mg of Chlortetracycline Hydrochloride add 2 mL of *sulfuric acid*; a deep blue colour is produced, which becomes bluish green. Add 1 mL of *water*; a brown colour is produced.

TESTS

Tetracycline hydrochloride and 4-epichlortetracycline hydrochloride

Not more than 8.0% and 6.0% respectively, determined as described under Assay. Inject separately solutions (1) and (4).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, *prepared immediately before use*

(1) Disperse a quantity of the ointment containing 25 mg of Chlortetracycline Hydrochloride in 20 mL of *chloroform* and 50 mL of 0.01M *hydrochloric acid* and shake for 15 minutes. Dilute to 100 mL with 0.01M *hydrochloric acid*, mix thoroughly, allow to separate and filter the aqueous layer.

(2) Dissolve 25 mg of *chlortetracycline hydrochloride BPCRS* in 20 mL of *chloroform* and 50 mL of 0.01M *hydrochloric acid* and shake for 15 minutes. Dilute to 100 mL with 0.01M *hydrochloric acid*, mix thoroughly, allow to separate and filter the aqueous layer.

(3) 0.025% w/v of each of *chlortetracycline hydrochloride BPCRS* and *4-epichlortetracycline hydrochloride* in 0.01M *hydrochloric acid*.

(4) 0.002% w/v of *tetracycline hydrochloride BPCRS* and 0.0015% w/v of *4-epichlortetracycline hydrochloride* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 355 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *dimethylformamide* and 80 volumes of 0.1M *oxalic acid* the pH of which has been adjusted to 2.2 with *triethylamine*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 1.5.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{22}H_{23}ClN_2O_8$,HCl in the ointment using the declared content of $C_{22}H_{23}ClN_2O_8$,HCl in *chlortetracycline hydrochloride BPCRS*.

STORAGE

Chlortetracycline Ointment should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

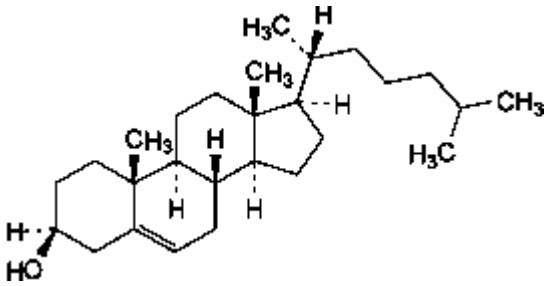
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Cholesterol

General Notices

(Ph. Eur. monograph 0993)



$C_{27}H_{46}O$ 386.7 *57-88-5*

Action and use

Excipient.

Ph Eur

DEFINITION

Cholest-5-en-3β-ol.

Content

— *cholesterol*: minimum 95.0 per cent (dried substance);

— *total sterols*: 97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in acetone and in ethanol (96 per cent).

It is sensitive to light.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 147 °C to 150 °C.

B. Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use*.

Test solution Dissolve 10 mg of the substance to be examined in *ethylene chloride R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 10 mg of *cholesterol CRS* in *ethylene chloride R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *ethyl acetate R*, *toluene R* (33:66 *V/V*).

Application 20 µL.

Development Immediately, protected from light, over a path of 15 cm.

Drying In air.

Detection Spray 3 times with *antimony trichloride solution R*; examine within 3-4 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve about 5 mg in 2 mL of *methylene chloride R*. Add 1 mL of *acetic anhydride R*, 0.01 mL of *sulfuric acid R* and shake. A pink colour is produced which rapidly changes to red, then to blue and finally to brilliant green.

TESTS

Solubility in ethanol (96 per cent)

In a stoppered flask, dissolve 0.5 g in 50 mL of *ethanol (96 per cent) R* at 50 °C. Allow to stand for 2 h. No deposit or turbidity is formed.

Acidity

Dissolve 1.0 g in 10 mL of *ether R*, add 10.0 mL of *0.1 M sodium hydroxide* and shake for about 1 min. Heat gently to eliminate ether and then boil for 5 min. Cool, add 10 mL of *water R* and 0.1 mL of *phenolphthalein solution R* as indicator and titrate with *0.1 M hydrochloric acid* until the pink colour just disappears, stirring the solution vigorously throughout the titration. Carry out a blank titration. The difference between the volumes of *0.1 M hydrochloric acid* required to change the colour of the indicator in the blank and in the test is not more than 0.3 mL.

Loss on drying (2.2.32)

Maximum 0.3 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Gas chromatography (2.2.28).

Internal standard solution Dissolve 0.100 g of *pregnenolone isobutyrate CRS* in *heptane R* and dilute to 100.0 mL with the same solvent.

Test solution Dissolve 25.0 mg of the substance to be examined in the internal standard solution and dilute to 25.0 mL with the same solution.

Reference solution Dissolve 25.0 mg of *cholesterol CRS* in the internal standard solution and dilute to 25.0 mL with the same solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2 mL/min.

Split ratio 1:25.

Temperature:

— *column*: 275 °C;

— *injection port*: 285 °C;

— *detector*: 300 °C.

Detection Flame ionisation.

Injection 1.0 µL.

System suitability Reference solution:

— *resolution*: minimum 10.0 between the peaks due to pregnenolone isobutyrate and cholesterol;

— *symmetry factor*: minimum 0.6 for the peak due to cholesterol.

Calculate the percentage content of cholesterol taking into account the assigned content of *cholesterol CRS*. Calculate the percentage content of total sterols by adding together the contents of cholesterol and other substances with a retention time less than or equal to 1.5 times the retention time of cholesterol. Disregard the peaks due to the internal standard and the solvent.

STORAGE

Protected from light.

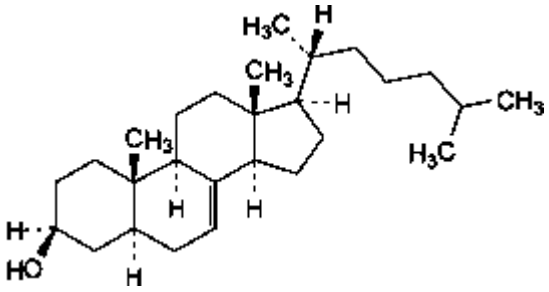
LABELLING

www.webofpharma.com

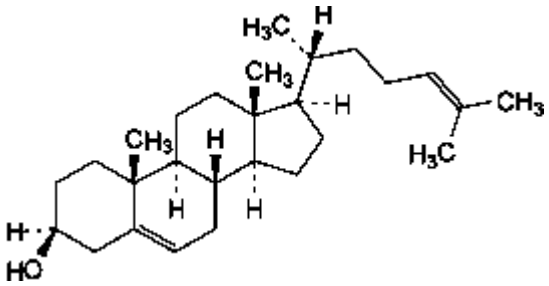
https://thuvienthuocngocanh.com/

The label states the source material for the production of cholesterol (for example bovine brain and spinal cord, wool fat or chicken eggs).

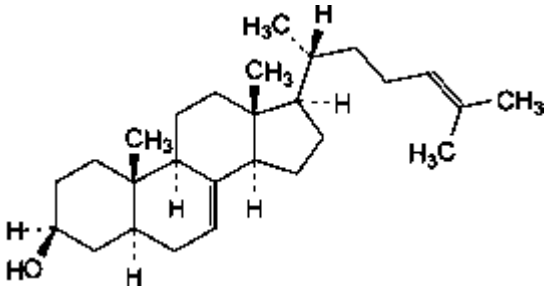
IMPURITIES



A. 5α-cholest-7-en-3β-ol (lathosterol),



B. cholesta-5,24-dien-3β-ol (desmosterol),



C. 5α-cholesta-7,24-dien-3β-ol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

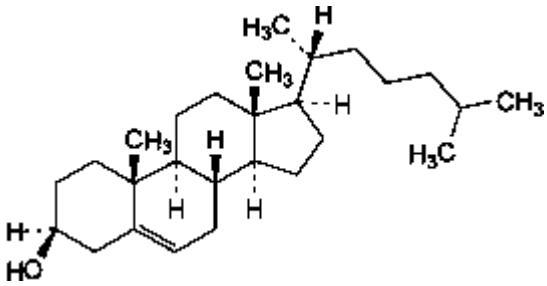
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Cholesterol for Parenteral Use

General Notices

(Ph. Eur. monograph 2397)



$C_{27}H_{46}O$ 386.7 *57-88-5*

Action and use

Excipient.

Ph Eur

DEFINITION

Cholest-5-en-3β-ol obtained from *Wool fat (0134)* or produced by synthetic means from plant-derived raw materials.

Content

— *cholesterol*: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in acetone and in ethanol (96 per cent).

It is sensitive to light.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *cholesterol CRS*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

TESTS

The tests for other sterols and for benzoyl ureas only apply to cholesterol for parenteral use obtained from wool fat. The test for related substances only applies to cholesterol for parenteral use of synthetic origin.

Solubility in ethanol (96 per cent)

In a stoppered flask, dissolve 0.5 g in 50 mL of *ethanol (96 per cent) R* at 50 °C. Allow to stand for 2 h. The solution is clear.

Peroxide value (2.5.5, Method A)

Maximum 10.

Other sterols

Gas chromatography (2.2.28): use the normalisation procedure.

Internal standard solution Dissolve 0.100 g of *pregnenolone isobutyrate CRS* in *heptane R* and dilute to 100.0 mL with the same solvent.

Test solution Dissolve 25.0 mg of the substance to be examined in the internal standard solution and dilute to 25.0 mL with the same solution.

Reference solution Dissolve 25.0 mg of *cholesterol CRS* in the internal standard solution and dilute to 25.0 mL with the same solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2 mL/min.

Split ratio 1:25.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

— *column*: 275 °C;

— *injection port*: 285 °C;

— *detector*: 300 °C.

Detection Flame ionisation.

Injection 1.0 µL.

Relative retention With reference to cholesterol (retention time = about 8.5 min): pregnenolone isobutyrate = about 0.8.

System suitability Reference solution:

— *resolution*: minimum 10.0 between the peaks due to pregnenolone isobutyrate and cholesterol.

Limits:

— *total of other substances with a retention time less than or equal to 1.5 times the retention time of cholesterol*: maximum 0.5 per cent;

— *disregard limit*: 0.05 per cent; disregard the peak due to the internal standard.

Benzoyl ureas

Liquid chromatography (*2.2.29*).

Test solution Dissolve 1.0 g of the substance to be examined in 200 mL of *heptane R* using a magnetic stirrer and add 10 mL of *acetonitrile R*. Shake and allow the layers to separate. Separate the lower layer (acetonitrile) and add 10 mL of *acetonitrile R* to the heptane layer and extract again. Combine the lower layers and evaporate to dryness by suitable means. Add 0.5 mL of *acetonitrile R* then 0.5 mL of *water R* to the residue. Suspend with the aid of ultrasound for about 5 min. Centrifuge the suspension for 5 min and use the supernatant.

Reference solution (a) Dissolve 10.0 mg of *diflubenzuron R* (impurity A) and 10.0 mg of *triflumuron R* (impurity B) in *acetonitrile R* and dilute to 100.0 mL with the same solvent. Dilute 0.1 mL of the solution to 100.0 mL with *acetonitrile R*.

Reference solution (b) Mix 0.5 mL of reference solution (a) and 0.5 mL of *water R*.

Reference solution (c) Dissolve 1.0 g of the substance to be examined in 200 mL of *heptane R* using a magnetic stirrer. Add 0.5 mL of reference solution (a) and 9.5 mL of *acetonitrile R*. Shake and allow the layers to separate. Separate the lower layer (acetonitrile) and add 10 mL of *acetonitrile R* to the heptane layer and extract again. Combine the lower layers and evaporate to dryness by suitable means. Add 0.5 mL of *acetonitrile R* then 0.5 mL of *water R* to the residue. Suspend with the aid of ultrasound for about 5 min. Centrifuge the suspension for 5 min and use the supernatant.

Column:

— *size*: *l* = 0.25 m, Ø = 3 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water for chromatography R* (50:50 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 20.5	100 → 0	0 → 100
20.5 - 30	0	100

After elution of the components, a gradient is applied to prevent a strong drifting baseline due to cholesterol during the following run.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 100 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Retention time Impurity A = about 10 min; impurity B = about 18 min.

Limits:

— *impurity A*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.05 ppm);

— *impurity B*: not more than 0.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.05 ppm).

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Derivatisation solution Mix 40 volumes of *N,O-bis(trimethylsilyl)trifluoroacetamide R* containing 1 per cent *V/V* of *chlorotrimethylsilane R* with 60 volumes of *anhydrous pyridine R*.

Blank solution Derivatisation solution.

Test solution To 25.0 mg of the substance to be examined add 1.0 mL of the derivatisation solution and promptly crimp-seal the vial. Mix and allow to stand at room temperature for at least 30 min.

Reference solution (a) Dissolve 5 mg of *campesterol R* (impurity C) and 5 mg of *β-sitosterol for peak identification CRS* (impurity D) in *anhydrous pyridine R* and dilute to 5 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) To 25 mg of *cholesterol CRS* add 100 µL of reference solution (a) and 1 mL of the derivatisation solution and promptly crimp-seal the vial. Mix and allow to stand at room temperature for at least 30 min.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	250 → 280
	5 - 35	280
Injection port		280
Detector		280

Detection Flame ionisation.

Injection 1 µL of the test solution, blank solution and reference solution (b).

Identification of peaks Use the chromatogram obtained with reference solution (b) to identify the peaks due to the cholesterol derivative and to the derivatives of impurities C and D.

Relative retention With reference to the cholesterol derivative (retention time = about 14 min): impurity C derivative = about 1.2; impurity D derivative = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 8.0 between the peaks due to the cholesterol derivative and the impurity C derivative.

Limits:

— *impurities C and D*: for each impurity, maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.1 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

ASSAY

Gas chromatography (2.2.28) as described in the test for other sterols with the following modification:

System suitability Reference solution:

— *symmetry factor*: minimum 0.6.

Calculate the percentage content of $C_{27}H_{46}O$ taking into account the assigned content of *cholesterol CRS*.

STORAGE

Protected from light.

LABELLING

The label states the origin of the substance.

IMPURITIES

Test for benzoyl ureas

A, B.

Specified impurities *A, B.*

Test for related substances

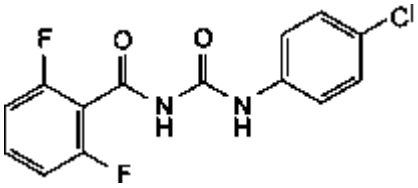
C, D, E, F.

Specified impurities *C, D.*

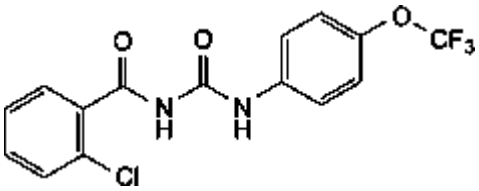
www.webofpharma.com

https://thuocngocanh.com/

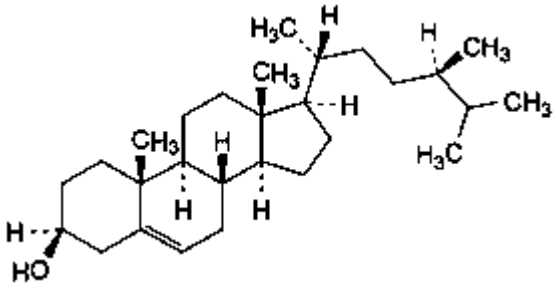
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F.*



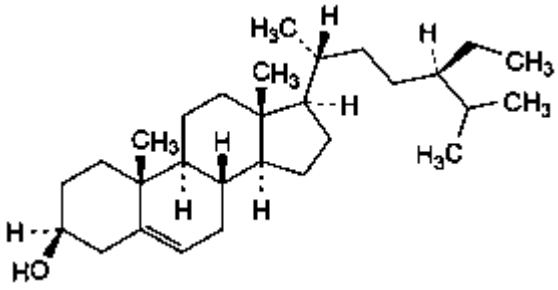
A. *N*-[(4-chlorophenyl)carbamoyl]-2,6-difluorobenzamide (diflubenzuron),



B. 2-chloro-*N*-[[4-(trifluoromethoxy)phenyl]carbamoyl]benzamide (triflumuron),



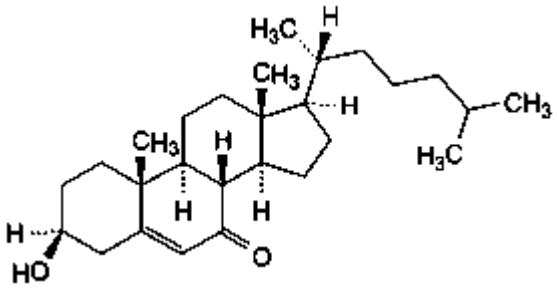
C. (24*R*)-ergost-5-en-3β-ol (campesterol),



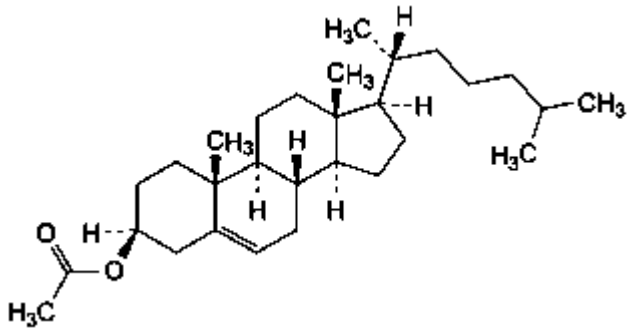
D. stigmast-5-en-3β-ol (β-sitosterol),

www.webofpharma.com

https://thuocngocanh.com/



E. 3β-hydroxycholest-5-en-7-one (7-ketocholesterol),



F. cholest-5-en-3β-yl acetate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Choline Salicylate Ear Drops

General Notices

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Choline Salicylate Ear Drops are a solution of choline salicylate in Propylene Glycol. They are prepared by diluting Choline Salicylate Solution.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of choline salicylate, $C_{12}H_{19}NO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Heat 2 mL with *sodium hydroxide* until fumes are evolved. Triethylamine vapour is evolved, which turns moist *red litmus paper* blue.

B. Dilute a quantity containing 2 g of choline salicylate to 20 mL with *water*. The resulting solution yields the reactions characteristic *of salicylates*, Appendix VI.

ASSAY

To a quantity containing 0.4 g of choline salicylate add 50 mL of *1,4-dioxan* and 5 mL of *acetic anhydride* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.25 mL of *methyl orange-xylene cyanol FF solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 24.13 mg of $C_{12}H_{19}NO_4$.

LABELLING

The strength is stated as the percentage w/v of choline salicylate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

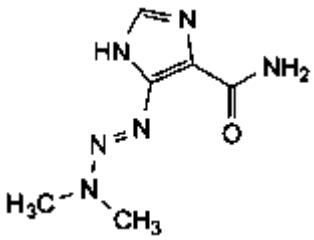
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dacarbazine

General Notices

(Ph. Eur. monograph 1691)



$C_6H_{10}N_6O$ 182.2 *4342-03-4*

Action and use

Cytotoxic alkylating agent.

Ph Eur

DEFINITION

5-[(1*E*)-3,3-Dimethyltriaz-1-en-1-yl]-1*H*-imidazole-4-carboxamide.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder.

Solubility

Slightly soluble in water and in anhydrous ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 15.0 mg in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same solution. Dilute 5.0 mL of the solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Spectral range 200-400 nm.

Absorption maximum 323 nm.

Shoulder 275 nm.

Specific absorbance at the absorption maximum 1024 to 1131.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dacarbazine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 2.0 mg of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 2.0 mg of *dacarbazine CRS* in *methanol R* and dilute to 5.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (10:20:50 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Dissolve 0.25 g in a 210 g/L solution of *citric acid monohydrate R* and dilute to 25.0 mL with the same solution.

Related substances

A. Liquid chromatography (2.2.29). *Use freshly prepared solutions and protect them from light. Use freshly prepared mobile phase as it contains sodium dioctyl sulfosuccinate.*

www.webofpharma.com

https://thuocngocanh.com/

Flush the column with a mixture of equal volumes of *methanol R* and *water for chromatography R* for at least 2 h at the end of each day or after all tests have been completed.

Test solution Dissolve 50.0 mg of the substance to be examined and 75 mg of *citric acid monohydrate R* in *distilled water R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *distilled water R*.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *distilled water R*.

Reference solution (c) Dissolve 5.0 mg of *dacarbazine impurity A CRS* in *distilled water R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of this solution to 25.0 mL with *distilled water R*.

Reference solution (d) Dissolve 5.0 mg of *dacarbazine impurity B CRS* in *distilled water R* and dilute to 50.0 mL with the same solvent.

Reference solution (e) Dilute 1.0 mL of reference solution (d) to 10.0 mL with *distilled water R*.

Reference solution (f) Mix 1 mL of reference solution (a) and 1 mL of reference solution (d) and dilute to 10 mL with *distilled water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 15.63 g/L solution of *glacial acetic acid R* containing 2.33 g/L of *sodium dioctyl sulfosuccinate R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 25 µL of the test solution and reference solution (c).

Run time 3 times the retention time of impurity A.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Retention time Impurity A = about 3 min.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities eluting after impurity A*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent).

B. Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modifications.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 45 volumes of a 15.63 g/L solution of *glacial acetic acid R* containing 2.33 g/L of *sodium dioctyl sulfosuccinate R* and 55 volumes of *methanol R*.

Injection 10 µL of the test solution and reference solutions (b), (e) and (f).

Run time Twice the retention time of dacarbazine.

Identification of impurities Use the chromatogram obtained with reference solution (e) to identify the peak due to impurity B.

Relative retention With reference to dacarbazine (retention time = about 27 min): citric acid = about 0.05; impurity B = about 0.8.

System suitability Reference solution (f):

— *resolution*: minimum 1.5 between the peaks due to impurity B and dacarbazine.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (e) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to dacarbazine in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the peak due to dacarbazine in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the peak due to dacarbazine in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to citric acid.

Impurity D

Gas chromatography (2.2.28). *Prepare the solutions immediately before use.*

Test solution Suspend 0.500 g of the substance to be examined in 5.0 mL of *ethyl acetate R1*. Filter through a membrane filter (nominal pore size 0.45 µm).

Reference solution Dilute 1.250 g of a 40 per cent *m/m* solution of *dimethylamine R* (equivalent to 0.500 g of impurity D) to 100.0 mL with *ethyl acetate R1*. Dilute 1.0 mL of the solution to 100.0 mL with *ethyl acetate R1*.

Column:

— *material*: fused silica;

— *size*: *l* = 30.0 m, Ø = 0.53 mm;

— *stationary phase*: *base-deactivated macrogol R* (film thickness 1.0 µm).

Carrier gas *helium for chromatography R*.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 3.0 mL/min.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	40
	1 - 6	40 → 50
	6 - 12	50 → 200
	12 - 22	200
Injection port		180
Detector		220

Detection Flame ionisation.

Injection 1.0 µL.

Retention time Impurity D = about 3 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 5.0 per cent for the area of the peak due to impurity D determined on 6 injections.

Calculation of percentage content:

— use the concentration of impurity D in the reference solution.

Limit:

— *impurity D*: maximum 0.05 per cent.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.150 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 18.22 mg of $C_6H_{10}N_6O$.

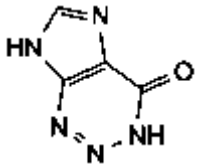
STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

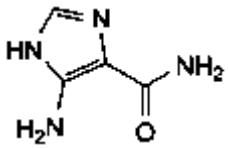
IMPURITIES

Specified impurities *A, B, D.*

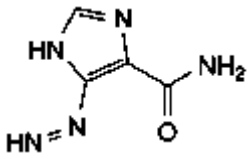
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



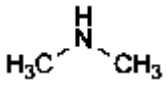
A. 3,7-dihydro-4*H*-imidazo[4,5-*d*][1,2,3]triazin-4-one (2-azahypoxanthine),



B. 5-amino-1*H*-imidazole-4-carboxamide,



C. 5-diazenyl-1*H*-imidazole-4-carboxamide,



D. *N*-methylmethanamine (dimethylamine).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dacarbazine Injection

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Dacarbazine Injection is a sterile solution of Dacarbazine in Water for Injections. It is prepared by dissolving Dacarbazine for Injection in the requisite amount of Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Dacarbazine Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

DACARBAZINE FOR INJECTION

DEFINITION

Dacarbazine for Injection is a sterile material consisting of Dacarbazine with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of dacarbazine, $C_6H_{10}N_6O$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A white or very pale yellow powder.

IDENTIFICATION

A. Dissolve a quantity of the contents of the sealed container containing 0.1 g of Dacarbazine in 200 mL of 0.1M *mixed phosphate buffer pH 7.0*, dilute with the buffer solution to 250 mL and dilute 3 mL to 200 mL with the same buffer solution. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 237 nm and 330 nm.

www.webofpharma.com

https://nhathuocngocanh.com/

B. In the test for 5-aminoimidazole-4-carboxamide hydrochloride, the principal peak in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (3).

TESTS

5-Aminoimidazole-4-carboxamide hydrochloride

Carry out the method for *liquid chromatography*, Appendix III D protected from light, using the following solutions in low-actinic glassware.

(1) Dissolve a quantity of the contents of the sealed container containing 0.20 g of Dacarbazine in 40 mL of 0.1M *acetic acid* and add sufficient 0.1M *acetic acid* to produce 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.1M *acetic acid*.

(3) 0.004% w/v of *dacarbazine BPCRS* in 0.1M *acetic acid*.

(4) 0.0024% w/v of *5-aminoimidazole-4-carboxamide hydrochloride* in 0.1M *acetic acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used using the mobile phase described below. Inject each sample within 1 hour of preparation.

MOBILE PHASE

0.005M *dioctyl sodium sulfosuccinate* in a mixture of 3 volumes of *glacial acetic acid*, 87 volumes of *water* and 110 volumes of *methanol*.

LIMITS

The area of any peak corresponding to 5-aminoimidazole-4-carboxamide hydrochloride in the chromatogram obtained with solution (1) is not greater than the area of the peak in the chromatogram obtained with solution (4) (0.6%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D protected from light, using the following solutions.

(1) Dissolve a quantity of the contents of the sealed container containing 0.20 g of Dacarbazine in 40 mL of 0.25M *acetic acid* and add sufficient 0.25M *acetic acid* to produce 50 mL.

(2) 0.0040% w/v of *2-azahypoxanthine BPCRS* in 0.25M *acetic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution within 1 hour of preparation.

(g) After use the column should be thoroughly flushed with *methanol* to remove dacarbazine which does not elute with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

0.005M *dioctyl sodium sulfosuccinate* in a mixture of 1.5 volumes of *glacial acetic acid* and 98.5 volumes of *water*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

not more than one such peak has an area greater than half the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all such peaks is not greater than three times the area of the peak in the chromatogram obtained with solution (2) (3%).

Uniformity of content

Sealed containers containing 200 mg or less of Dacarbazine comply with the requirements stated under Parenteral Preparations, Powders for Injections or Infusions. Use the individual results obtained in the Assay.

ASSAY

Carry out the following procedure protected from light. Dissolve the contents of one container in 0.1M *hydrochloric acid* and dilute with sufficient 0.1M *hydrochloric acid* to produce a final solution containing 0.0008% w/v of Dacarbazine. Measure the *absorbance* of the resulting solution at the maximum at 323 nm, Appendix II B. Calculate the content of $C_6H_{10}N_6O$ in the sealed container taking 1090 as the value of A(1%, 1 cm) at the maximum at 323 nm.

Repeat the procedure with a further nine sealed containers and calculate the average content of $C_6H_{10}N_6O$ per container from the 10 individual results thus obtained.

STORAGE

The sealed container should be protected from light and stored at a temperature of 2° to 8°.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

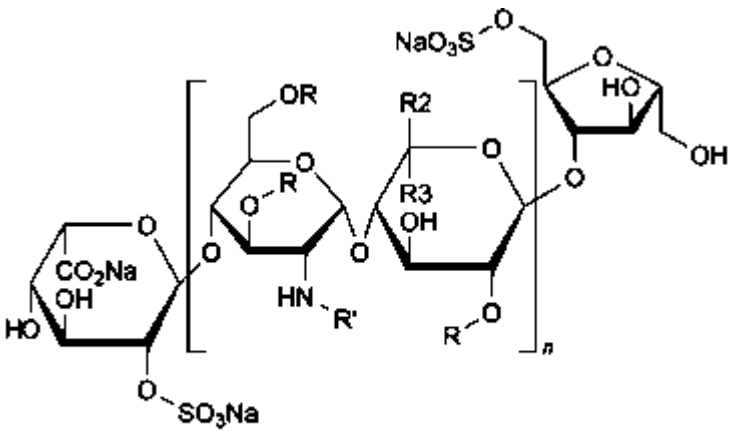
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dalteparin Sodium

General Notices

(Ph. Eur. monograph 1195)



Action and use

Low molecular weight heparin.

Preparation

Dalteparin Sodium Injection

Ph Eur

DEFINITION

Dalteparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by nitrous acid depolymerisation of heparin from porcine intestinal mucosa. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain.

Dalteparin sodium complies with the monograph Low-molecular-mass heparins (0828) with the modifications and additional requirements below.

The mass-average relative molecular mass ranges between 5600 and 6400, with a characteristic value of about 6000.

The degree of sulfatation is 2.0 to 2.5 per disaccharide unit.

The potency is not less than 110 IU and not more than 210 IU of anti-factor Xa activity per milligram, calculated with reference to the dried substance. The anti-factor IIa activity is not less than 35 IU/mg and not more than 100 IU/mg, calculated with reference to the dried

www.webofpharma.com

https://thuocngocanh.com/

substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.9 and 3.2.

PRODUCTION

Dalteparin sodium is produced by a validated manufacturing and purification procedure under conditions designed to minimise the presence of N-NO groups.

The manufacturing procedure must have been shown to reduce any contamination by N-NO groups to approved limits using an appropriate, validated quantification method.

IDENTIFICATION

Carry out identification test A as described in the monograph *Low-molecular-mass heparins (0828)* using *dalteparin sodium CRS*.

Carry out identification test C as described in the monograph *Low-molecular-mass heparins (0828)*. The following requirements apply.

The mass-average relative molecular mass ranges between 5600 and 6400. The mass percentage of chains lower than 3000 is not more than 13.0 per cent. The mass percentage of chains higher than 8000 ranges between 15.0 per cent and 25.0 per cent.

TESTS

Appearance of solution

Dissolve 1 g in 10 mL of *water R*. The solution is clear (*2.2.1*) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Nitrite

Not more than 5 ppm. Examine by liquid chromatography (*2.2.29*). *Rinse all volumetric flasks at least three times with water R before the preparation of the solutions.*

Test solution Dissolve 80.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent. Allow to stand for at least 30 min.

Reference solution (a) Dissolve 60.0 mg of *sodium nitrite R* in *water R* and dilute to 1000.0 mL with the same solvent.

For the preparation of reference solution (b), use a pipette previously rinsed with reference solution (a).

Reference solution (b) Dilute 1.00 mL of reference solution (a) to 50.0 mL with *water R*.

Before preparing reference solutions (c), (d) and (e), rinse all pipettes with reference solution (b).

Reference solution (c) Dilute 1.00 mL of reference solution (b) to 100.0 mL with *water R* (corresponding to 1 ppm of nitrite in the test sample).

Reference solution (d) Dilute 3.00 mL of reference solution (b) to 100.0 mL with *water R* (corresponding to 3 ppm of nitrite in the test sample).

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (e) Dilute 5.00 mL of reference solution (b) to 100.0 mL with *water R* (corresponding to 5 ppm of nitrite in the test sample).

The chromatographic procedure may be carried out using:

— a column 0.125 m long and 4.3 mm in internal diameter packed with a strong anion-exchange resin;

— as mobile phase at a flow rate of 1.0 mL/min a solution consisting of 13.61 g of *sodium acetate R* dissolved in *water R*, adjusted to pH 4.3 with *phosphoric acid R* and diluted to 1000 mL with *water R*;

— as detector an appropriate electrochemical device with the following characteristics and settings: a suitable working electrode, a detector potential of + 1.00 V versus Ag/AgCl reference electrode and a detector sensitivity of 0.1 µA full scale.

Inject 100 µL of reference solution (d). When the chromatograms are recorded in the prescribed conditions, the retention time for nitrite is 3.3 to 4.0 min. The test is not valid unless:

— the number of theoretical plates calculated for the nitrite peak is at least 7000 per metre per column (dalteparin sodium will block the binding sites of the stationary phase, which will cause shorter retention times and lower separation efficiency for the analyte; the initial performance of the column may be partially restored using a 58 g/L solution of *sodium chloride R* at a flow rate of 1.0 mL/min for 1 h; after regeneration the column is rinsed with 200 mL to 400 mL of *water R*);

— the symmetry factor for the nitrite peak is less than 3;

— the relative standard deviation of the peak area for nitrite obtained from 6 injections is less than 3.0 per cent.

Inject 100 µL each of reference solutions (c) and (e). The test is not valid unless:

— the correlation factor for a linear relationship between concentration and response for reference solutions (c), (d) and (e) is at least 0.995;

— the signal-to-noise ratio for reference solution (c) is not less than 5 (if the noise level is too high, electrode recalibration is recommended);

— a blank injection of *water R* does not give rise to spurious peaks.

Inject 100 µL of the test solution. Calculate the content of nitrite from the peak areas in the chromatogram obtained with reference solutions (c), (d) and (e).

Boron

Not more than 1 ppm, determined by inductively coupled plasma atomic emission spectroscopy.

Boron is determined by measurement of the emission from an inductively coupled plasma (ICP) at a wavelength specific to boron. The emission line at 249.733 nm is used. Use an appropriate apparatus, whose settings have been optimised as directed by the manufacturer.

Test solution Dissolve 0.2500 g of the substance to be examined in about 2 mL of *water for chromatography R*, add 100 µL of *nitric acid R* and dilute to 10.00 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Prepare a 1 per cent *V/V* solution of *nitric acid R* in *water for chromatography R* (blank).

Reference solution (b) Prepare a 11.4 µg/mL solution of *boric acid R* in a 1 per cent *V/V* solution of *nitric acid R* in *water for chromatography R* (STD_{cal}).

Reference solution (c) Dissolve 0.2500 g of a reference dalteparin sodium with no detectable boron in about 2 mL of *water for chromatography R*, add 100 µL of *nitric acid R* and dilute to 10.00 mL with the same solvent (STD_0).

Reference solution (d) Dissolve 0.2500 g of a reference dalteparin sodium with no boron detected in about 2 mL of a 1 per cent *V/V* solution of *nitric acid R* in *water for chromatography R*, add 10 µL of a 5.7 mg/mL solution of *boric acid R* and dilute to 10.00 mL with the same solvent (STD_1). This solution contains 1 µg/mL of boron.

Calculate the content of boron in the substance to be examined, using the following correction factor:

$$f = \frac{\left(STD_1 - STD_0\right) \times 2}{\left(STD_{cal} - blank\right)}$$

Loss on drying (*2.2.32*)

Not more than 5.0 per cent, determined on 1.000 g by drying in an oven at 60 °C over *diphosphorus pentoxide R* at a pressure not exceeding 670 Pa for 3 h.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dalteparin Sodium Injection

General Notices

Action and use

Low molecular weight heparin.

DEFINITION

Dalteparin Sodium Injection is a sterile solution of Dalteparin Sodium in Water for Injections.

PRODUCTION

The final product is produced by methods of manufacturing designed to ensure that substances lowering blood pressure are not introduced and to ensure freedom from contamination by over-sulfated glycosaminoglycans. The production method is validated to demonstrate that the product if tested, would comply with the test for Related substances given below.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Activity

The estimated activity for anti-factor Xa is not less than 90% and not more than 110% of the stated activity.

The ratio of anti-factor Xa to anti-factor IIa is not less than 1.9 and not more than 3.2.

CHARACTERISTICS

A clear, colourless or straw-coloured liquid.

IDENTIFICATION

A. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions in the mobile phase.

(1) Dilute the injection to contain 1600 units of anti-factor Xa per mL.

(2) 1% w/v of *heparin low-molecular-mass for calibration EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a column (30 cm × 7.8 mm) packed with appropriate porous silica beads (5 µm) with a fractionation range for proteins of approximately 15 000 to 100 000 Da (Tosoh Bioscience TSK-GEL G2000SWXL or TSK-GEL G3000SWXL are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use an ambient column temperature.

(e) For detection use a differential refractometer (RI).

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 25 µL of each solution.

To calibrate, inject 25 µL of the reference solution and record the chromatogram for a period of time, ensuring complete elution of sample, salt and solvent peaks. Calculate the total area under the RI curve (ΣRI) by numerical integration over the range of interest (i.e. excluding salt and solvent peaks at the end of the chromatogram as well as the artefact peak (*), that if present, elutes at the same retention time as the peak that would be obtained after injection of sodium sulfate) as shown in Figure 1.

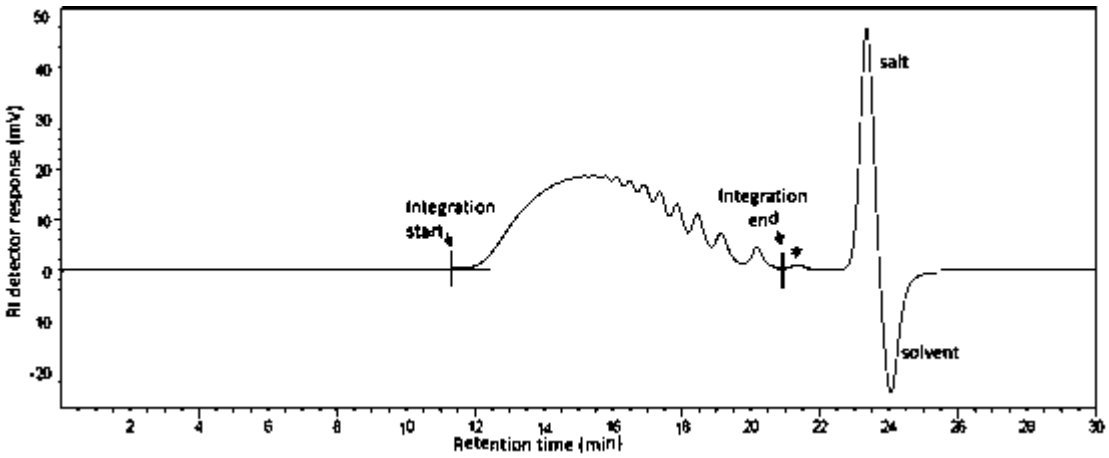


Figure 1 - Example chromatogram of a low-molecular-mass heparin sample analysed using the method described in identification test A indicating peak integration

Calculate the area under the curve up to each point as a percentage of the total area.

Using the leaflet supplied with *heparin low-molecular-mass for calibration EPCRS*, identify those points in the chromatogram for which the percentage of the total area under the curve is closest to the percentage mass fractions listed in the Broad Standard Table, and assign the molecular mass in the table to the corresponding retention time in the chromatogram. A calibration curve for the chromatographic system is derived by fitting a suitable mathematical relationship to the set of retention times and logarithms of the molecular masses. A polynomial of the 3rd degree is recommended.

Inject 25 µL of the test solution and record the chromatogram for a sufficient period of time to ensure complete elution of sample, salt and solvent peaks.

The mass-average relative molecular mass is defined by the following expression:

$$\frac{\sum \left(\mathrm{RI}_i M_i \right)}{\sum \mathrm{RI}_i}$$

where:

RI_i	=	Refractive Index of substance eluting in the fraction *i* (proportional to the mass of the substance);
M_i	=	relative molecular mass corresponding to fraction *i*.

MOBILE PHASE

0.77% w/v of *ammonium acetate*.

www.webofpharma.com

https://thuocngocanh.com/

CONFIRMATION

The mass-average relative molecular mass ranges between 5600 and 6400. The mass percentage of chains lower than 3000 is not more than 13.0%. The mass percentage of chains higher than 8000 ranges between 15.0% and 25.0%.

B. The ratio of anti-factor Xa activity to anti-factor IIa activity, determined as described under Assay, is not less than 1.9 and not more than 3.2.

C. Yields reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH, 5.0 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions. Solutions (3) to (6) are stable at room temperature for 24 hours.

(1) Dilute the injection with *water for chromatography* to give 5000 IU of anti-factor Xa per mL. Mix using a vortex mixer until dissolution is complete.

(2) Mix 500 µL of solution (1) and 250 µL of *1M hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of *1M sodium hydroxide* to stop the reaction.

(3) Dissolve 0.25 g of *heparin for physico-chemical analysis EPCRS* in *water for chromatography* and dilute to 2 mL with the same solvent. Mix using a vortex mixer until dissolution is complete.

(4) Add 1200 µL of solution (3) to 300 µL of *dermatan sulfate and over-sulfated chondroitin sulfate EPCRS*. Mix using a vortex mixer to homogenise.

(5) Add 400 µL of solution (3) to 100 µL of *water for chromatography* and mix using a vortex mixer. Add 250 µL of *1M hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of *1M sodium hydroxide* to stop the reaction.

(6) To 500 µL of solution (4), add 250 µL of *1M hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of *1M sodium hydroxide* to stop the reaction.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 2 mm) packed with *anion-exchange resin* (9 µm) (Dionex Ionpac AS11-HC is suitable) and a stainless steel pre-column (5 cm × 2 mm) packed with *anion-exchange resin* (13 µm) (Dionex Ionpac AG11-HC is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.22 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 202 nm.

(f) Inject 20 µL of solutions (2), (5) and (6).

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase A 0.040% w/v of *sodium dihydrogen orthophosphate* in *water for chromatography* adjusted to pH 3.0 with *dilute orthophosphoric acid*.

Mobile phase B 0.040% w/v of *sodium dihydrogen orthophosphate* and 14% w/v of *sodium perchlorate* in *water for chromatography*, adjusted to pH 3.0 with *dilute orthophosphoric acid*, filtered and degassed.

Equilibrate the column with the mobile phases in the initial gradient ratio for at least 15 minutes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	75	25	isocratic
10-35	75→0	25→100	linear gradient
35-40	0	100	isocratic
40-45	0→75	100→25	linear gradient
45-60	75	25	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to heparin (retention time about 26 minutes) are: dermatan sulfate/chondroitin sulfate, about 0.9 and over-sulfated chondroitin sulfate, 1.3.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (5) no peak is present at the retention time of heparin;

in the chromatogram obtained with solution (6) the *resolution* between the peaks due to dermatan sulfate/chondroitin sulfate and over-sulfated chondroitin sulfate is at least 3.0.

LIMITS

In the chromatogram obtained with solution (2):

the area of the peak due to dermatan sulfate/chondroitin sulfate is not greater than 0.3 times the area of the corresponding peak in the chromatogram obtained with solution (6) (2.0%);

no peaks other than the peak due to dermatan sulfate and chondroitin sulfate are detected.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 0.01 IU per International Unit of anti-Xa activity.

ASSAY

The anticoagulant activity of low-molecular-mass heparins is determined *in vitro* by two assays which determine its ability to accelerate the inhibition of factor Xa (anti-Xa assay) and thrombin, factor IIa (anti-IIa assay), by antithrombin III.

www.webofpharma.com

https://thuocngocanh.com/

The International Units for anti-Xa and anti-IIa activity are the activities contained in a stated amount of the International Standard for low-molecular-mass heparin.

Heparin low-molecular-mass for assay EPBRP, calibrated in International Units by comparison with the International Standard using the two assays given below, is used as the reference preparation.

Provided the equivalence with the below methods is demonstrated, the volumes below can be adjusted in order to use automated methods.

For anti-factor Xa activity

Test solutions (1) to *(4)* Prepare a series of 4 independent dilutions of the injection being examined in *tris-chloride buffer pH 7.4;* the concentration range of the solutions should be within 0.025 IU to 0.2 IU of anti-factor Xa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Reference solutions (1) to *(4)* Prepare a series of 4 dilutions of the reference preparation of low-molecular-mass heparin in *tris-chloride buffer pH 7.4;* the concentration range of the solutions should be within 0.025 IU to 0.2 IU of anti-factor Xa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Label 16 tubes in duplicate: T1, T2, T3, T4 for the dilutions of the injection being examined and R1, R2, R3, R4 for the dilutions of the reference preparation. To each tube add 50 µL of *antithrombin III solution R1* and 50 µL of the appropriate dilution of the injection being examined, or the reference preparation. After each addition, mix but do not allow bubbles to form. Treating the tubes in the order R1, R2, R3, R4, T1, T2, T3, T4, T1, T2, T3, T4, R1, R2, R3, R4, allow to equilibrate at 37° (in a water-bath or heating block) for 1 minute and add to each tube 100 µL of *bovine factor Xa solution*. Incubate for exactly 1 minute and add 250 µL of *chromophore substrate R1*. Stop the reaction after exactly 4 minutes by adding 375 µL of *acetic acid*. Transfer the mixtures to semi-micro cuvettes and measure the *absorbance* at 405 nm, Appendix II B, using a suitable reading device. Determine the blank amidolytic activity at the beginning and at the end of the procedure in a similar manner, using *tris-chloride buffer pH 7.4* instead of the reference and test solutions; the 2 blank values do not differ significantly. Calculate the regression of the absorbance on log concentrations of the solutions of the injection being examined and of the reference preparation of low-molecular-mass heparins and calculate the potency of the substance being examined in International Units of anti-factor Xa activity per mL using the usual statistical methods for parallel-line assays.

For anti-factor IIa activity

Test solutions (1) to *(4)* Prepare a series of 4 independent dilutions of the injection being examined in *tris-chloride buffer pH 7.4*; the concentration range should be within 0.015 IU to 0.075 IU of anti-factor IIa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Reference solutions (1) to *(4)* Prepare a series of 4 independent dilutions of the reference preparation of low molecular-mass heparin in *tris-chloride buffer pH 7.4*; the concentration range should be within 0.015 IU to 0.075 IU of anti-factor IIa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Label 16 tubes in duplicate: T1, T2, T3, T4 for the dilutions of the injection being examined and R1, R2, R3, R4 for the dilutions of the reference preparation. To each tube add 50 µL of *antithrombin III solution R2* and 50 µL of the appropriate dilution of the injection being examined or the reference preparation. After each addition, mix but do not allow bubbles to form. Treating the tubes in the order R1, R2, R3, R4, T1, T2, T3, T4, T1, T2, T3, T4, R1, R2, R3, R4, allow to equilibrate at 37° (in a water-bath or heating block) for 1 minute and add to each tube 100 µL of *human thrombin solution*. Incubate for exactly 1 minute and add 250 µL of *chromophore substrate R2*. Stop the

www.webofpharma.com

https://thuocngocanh.com/

reaction after exactly 4 minutes by adding 375 µL of *acetic acid*. Transfer the mixtures to semi-micro cuvettes and measure the *absorbance* at 405 nm, Appendix II B, using a suitable reading device. Determine the blank amidolytic activity at the beginning and at the end of the procedure in a similar manner, using *tris-chloride buffer pH 7.4* instead of the reference and test solutions; the 2 blank values do not differ significantly. Calculate the regression of the absorbance on log concentrations of the solutions of the substance to be examined and of the reference preparation of low-molecular-mass heparins, and calculate the potency of the substance being examined in International Units of anti-factor IIa activity per mL using the usual statistical methods for parallel-line assays.

LABELLING

The label states the number of IU (Units) of anti-factor Xa per unit volume.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

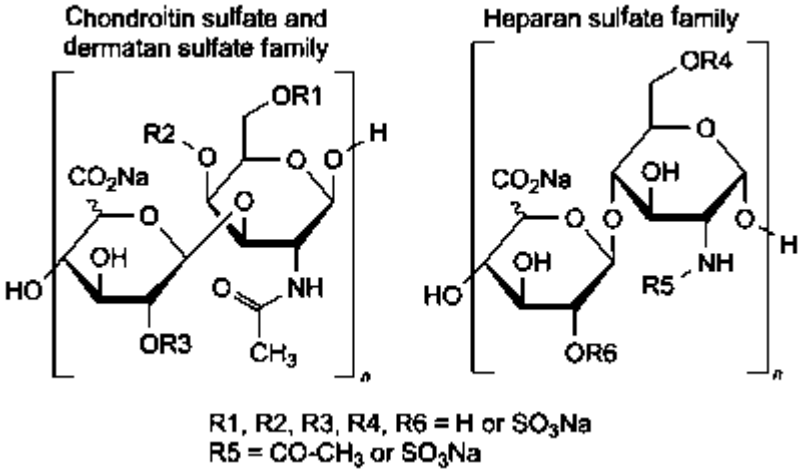
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Danaparoid Sodium

General Notices

(Ph. Eur. monograph 2090)



Action and use

Heparinoid; prevention of deep vein thrombosis.

Ph Eur

DEFINITION

Preparation containing the sodium salts of a mixture of sulfated glycosaminoglycans present in porcine tissues. Danaparoid sodium is prepared from the intestinal mucosa of pigs. Its major constituents are heparan sulfate and dermatan sulfate. On complete hydrolysis it liberates D-glucosamine, D-galactosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulfuric acid. It has the characteristic property of enhancing the inactivation of activated factor X (factor Xa) by antithrombin. It has a negligible effect on the inactivation rate of thrombin by antithrombin.

Potency

11.0 to 19.0 anti-factor Xa units per milligram (dried substance).

PRODUCTION

The animals from which danaparoid sodium is derived must fulfil the requirements for the health of animals suitable for human consumption. Danaparoid sodium is prepared using a process that ensures that the relative proportion of active sulfated

www.webofpharma.com

https://thuocngocanh.com/

glycosaminoglycans is consistent. It is produced by methods of manufacturing designed to minimise or eliminate endotoxins and hypotensive substances.

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water.

IDENTIFICATION

A. The ratio of anti-factor Xa activity to anti-factor IIa activity, determined as described under Assay and Tests respectively, is not less than 22.

B. Molecular mass distribution (see Tests): the mass-average relative molecular mass ranges between 4000 and 7000.

TESTS

pH (2.2.3)

5.5 to 7.0.

Dissolve 0.5 g of the dried substance to be examined in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Anti-factor IIa activity

Maximum 0.5 units per milligram (dried substance).

Carry out the test at room temperature. Human thrombin solution R1 must be kept on ice until use.

Test solutions Prepare 2 independent series of dilutions in geometric progression of the substance to be examined in *phosphate buffer solution pH 6.5 R* and in the concentration range of 0.0005-0.005 units of anti-factor IIa activity per millilitre.

Reference solutions Prepare 2 independent series of dilutions in geometric progression of *danaparoid sodium CRS* in *phosphate buffer solution pH 6.5 R* and in the concentration range of 0.0005-0.005 units of anti-factor IIa activity per millilitre.

Transfer 50 µL of each solution into the wells of a 96-well microplate. To each well add 50 µL of *antithrombin III solution R3* and 50 µL of *human thrombin solution R1*. Shake the microplate but do not allow bubbles to form. Incubate for 75 min. To each well add 50 µL of *chromogenic substrate R4*. Shake the microplate. Measure the absorbance at 405 nm (2.2.25) using a suitable reading device, exactly 2 min after the addition of the chromogenic substrate. Measure the absorbance again at 405 nm (2.2.25), exactly 22 min after the addition of the chromogenic substrate. Use ΔA ($A_{22} - A_2$) for the calculation of the anti-factor IIa activity. Determine the blank amidolytic activity in a similar manner, using *phosphate buffer solution pH 6.5 R* as the blank solution (minimum 8 blanks per microplate). Calculate the activity of the substance to be examined in units of anti-factor IIa activity per milligram using a suitable statistical method, for example the parallel-line assay (5.3).

www.webofpharma.com

https://thuocngocanh.com/

Chondroitin sulfate and dermatan sulfate

Chondroitin sulfate: maximum 8.5 per cent (dried substance); dermatan sulfate: 8.0 per cent to 16.0 per cent (dried substance).

Determine by selective enzymatic degradation.

Test solutions Dry the substance to be examined at 60 °C over *diphosphorus pentoxide R* at a pressure of about 670 Pa for 3 h. Dissolve 0.200 g of the dried substance in 10.0 mL of *water R*. Dilute this solution as necessary to obtain 3 test solutions containing 20 mg/mL, 10 mg/mL and 5 mg/mL of the dried substance to be examined in *water R*.

Chondroitin sulfate reference solutions Dry *chondroitin sulfate sodium CRS* over *diphosphorus pentoxide R* at room temperature at a pressure of about 670 Pa for 16 h. Prepare solutions containing 1 mg/mL, 2 mg/mL and 3 mg/mL of dried *chondroitin sulfate sodium CRS* in *water R*.

Dermatan sulfate reference solutions Dry *dermatan sulfate CRS* over *diphosphorus pentoxide R* at room temperature at a pressure of about 670 Pa for 16 h. Prepare solutions containing 1 mg/mL, 2 mg/mL and 3 mg/mL of dried *dermatan sulfate CRS* in *water R*.

Chondroitinase ABC solution Dissolve *chondroitinase ABC R* in *tris-sodium acetate-sodium chloride buffer solution pH 8.0 R* to obtain an activity of 0.5-1.0 units per millilitre.

Chondroitinase AC solution Dissolve *chondroitinase AC R* in *tris-sodium acetate-sodium chloride buffer solution pH 7.4 R* to obtain an activity of 1.0-2.0 units per millilitre.

Procedure:

— *Degradation with chondroitinase ABC*. Label 2 sets of 10 tubes in triplicate: T1, T2 and T3 for the test solutions; SD1, SD2 and SD3 for the dermatan sulfate reference solutions; SC1, SC2 and SC3 for the chondroitin sulfate reference solutions; and B for the blank (*water R*). To each tube add 1.25 mL of *tris-sodium acetate buffer solution pH 8.0 R* and 150 µL of the test solutions, dermatan sulfate reference solutions, chondroitin sulfate reference solutions or *water R*. To each tube in 1 set of tubes add 75 µL of chondroitinase ABC solution. To determine the blank response level, add 75 µL of *tris-sodium acetate-sodium chloride buffer solution pH 8.0 R* to each tube in the other set of tubes. Mix the contents of the tubes using a vortex mixer, cover with appropriate stoppers and incubate at 37 °C for at least 24 h.

— *Degradation with chondroitinase AC*. Label 7 tubes in triplicate: T1, T2 and T3 for the test solutions; SC1, SC2 and SC3 for the chondroitin sulfate reference solutions; and B for the blank (*water R*). To each tube add 1.25 mL of *tris-sodium acetate buffer solution pH 7.4 R* and 150 µL of the test solutions, chondroitin sulfate reference solutions or *water R*. Add 75 µL of chondroitinase AC solution to each tube. Mix the contents of the tubes using a vortex mixer, cover with appropriate stoppers and incubate at 37 °C for at least 24 h.

After the incubation period mix the contents of the tubes using a vortex mixer and dilute to 12 times with *water R*. Measure the absorbances (*2.2.25*) of the diluted solutions at 234 nm against *water R* using a suitable spectrophotometer.

Calculation Calculate the mean blank absorbance of each reference solution, i.e. the mean of the absorbances of the reference solutions to which no chondroitinase ABC has been added. Subtract the mean blank absorbance value from the individual absorbance of each reference solution. Calculate linear regression curves for the chondroitin sulfate reference solutions and the dermatan sulfate reference solutions by plotting the blank-corrected absorbances against the concentrations.

www.webofpharma.com

https://thuocngocanh.com/

Calculate the average percentage content of dermatan sulfate in the test solutions for all tested concentrations using the following expression:

$$\frac{A_2 - A_1 - \frac{\left(A_3 - A_1 - I_1\right) \times B_2}{B_1} - I_2 - I_3}{B_3 \times C} \times 100$$

A_1 = blank absorbance of the test solution;

A_2 = absorbance of the test solution with chondroitinase ABC;

A_3 = absorbance of the test solution with chondroitinase AC;

B_1 = gradient of the curve obtained with the chondroitin sulfate reference solutions with chondroitinase AC;

B_2 = gradient of the curve obtained with the chondroitin sulfate reference solutions with chondroitinase ABC;

B_3 = gradient of the curve obtained with the dermatan sulfate reference solutions with chondroitinase ABC;

C = concentration of the test solution, in milligrams per millilitre;

I_1 = y-intercept of the curve obtained with the chondroitin sulfate reference solutions with chondroitinase AC;

I_2 = y-intercept of the curve obtained with the chondroitin sulfate reference solutions with chondroitinase ABC;

I_3 = y-intercept of the curve obtained with the dermatan sulfate reference solutions with chondroitinase ABC.

Calculate the average percentage content of chondroitin sulfate in the test solutions for all tested concentrations using the following expression:

$$\frac{\left(A_3 - A_1 - I_1\right)}{B_1 \times C} \times 100$$

Molecular mass distribution

Size-exclusion chromatography (2.2.30).

Test solution Dissolve 10 mg of the substance to be examined in 2 mL of the mobile phase.

Reference solution Dissolve 10 mg of *danaparoid sodium CRS* in 2 mL of the mobile phase.

Column:

— *size*: *l* = 0.60 m, Ø = 7.5 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (10 µm) with a fractionation range for proteins with a relative molecular mass of approximately 5000 to 100 000;

— *temperature*: 30 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase 28.4 g/L solution of *anhydrous sodium sulfate R* adjusted to pH 5.0 with *dilute sulfuric acid R*.

Flow rate 0.9 mL/min ± 2 per cent.

Detection Spectrophotometer at 210 nm.

Injection 100 µL.

Run time For a period of time ensuring complete elution of sample and solvent peaks (about 40 min).

System suitability Inject the reference solution twice; the difference between the retention times corresponding to the maxima of the peaks is not more than 5 s.

Calibration Calibration is achieved by taking the relevant part of the chromatogram obtained with the reference solution, i.e. excluding the sharp peak at the end of the chromatogram, and matching the chromatogram obtained with the test solution with the calibration table obtained with the reference solution. From the calibration curve obtained, determine the molecular mass distribution of the sample. A calibration table is supplied with *danaparoid sodium CRS*.

Limits:

— *chains with a relative molecular mass less than 2000*: maximum 13 per cent;

— *chains with a relative molecular mass less than 4000*: maximum 39 per cent;

— *chains with a relative molecular mass between 4000 and 8000*: minimum 50 per cent;

— *chains with a relative molecular mass higher than 8000*: maximum 19 per cent;

— *chains with a relative molecular mass higher than 10 000*: maximum 11 per cent.

Nitrogen (*2.5.9*)

2.4 per cent to 3.0 per cent (dried substance).

Nucleic acids

Maximum 0.5 per cent (dried substance).

Test solution Weigh about 50 mg of the dried substance to be examined into a centrifuge tube and dissolve in 200 µL of *water R*.

Reference solution Dissolve about 50 mg of *ribonucleic acid CRS* in 5 mL of *0.1 M sodium hydroxide* and dilute to 20.0 mL with *water R*. Transfer 200 µL of the solution into a centrifuge tube.

Add 4.0 mL of a 50 g/L solution of *trichloroacetic acid R* to each tube and mix. Place all tubes in boiling water for 30 min. Allow to cool to room temperature. Add again 4.0 mL of a 50 g/L solution of *trichloroacetic acid R* to each tube and mix. If any of the test solutions is not clear, sonicate all the tubes in an ultrasonic bath for 10 min and centrifuge at 1500 *g* for 15 min. Dilute 1.0 mL of the clear supernatant to 4.0 mL with *water R*. Measure the absorbances of the diluted reference and test solutions at 265 nm (*2.2.25*) against a blank solution prepared in the same manner, and calculate the percentage nucleic acid content of the sample.

www.webofpharma.com

https://thuocngocanh.com/

Total protein (*2.5.33, Method 2*)

Maximum 0.5 per cent.

Dissolve the substance to be examined in *distilled water R*. Use *bovine albumin R1* as the reference substance.

Adjust the concentration of the diluted phosphomolybdotungstic reagent so that the pH in the reaction mixture is between 10.0 and 10.5.

Sodium

9.0 per cent to 11.0 per cent (dried substance).

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 0.125 g of the substance to be examined in 100.0 mL of a 1.27 mg/mL solution of *caesium chloride R* in *0.1 M hydrochloric acid*.

Reference solutions Prepare reference solutions containing 50 ppm, 100 ppm and 150 ppm of Na by diluting *sodium standard solution (1000 ppm Na) R* with a 1.27 mg/mL solution of *caesium chloride R* in *0.1 M hydrochloric acid*.

Source Sodium hollow-cathode lamp.

Wavelength 330.3 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 0.500 g by drying in an oven at 60 °C over *diphosphorus pentoxide R* at a pressure of 670 Pa for 3 h.

Bacterial endotoxins (*2.6.14*)

Less than 0.02 IU per unit of anti-factor Xa activity, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Carry out the assay at room temperature.

The anticoagulant activity of danaparoid sodium is determined *in vitro* by an assay which determines its ability to accelerate the inhibition of factor Xa by antithrombin III (anti-factor Xa assay).

Test solutions Prepare 2 independent series of dilutions in geometric progression of the substance to be examined in *tris(hydroxymethyl)aminomethane EDTA buffer solution pH 8.4 R* and in the concentration range of 0.1-0.32 units of anti-factor Xa activity per millilitre.

Reference solutions Prepare 2 independent series of dilutions in geometric progression of *danaparoid sodium CRS* in *tris(hydroxymethyl)aminomethane EDTA buffer solution pH 8.4 R* and in the concentration range of 0.08-0.35 units of anti-factor Xa activity

www.webofpharma.com

https://thuocngocanh.com/

per millilitre.

Transfer 40 µL of each solution into the wells of a 96-well microplate. Add 40 µL of *antithrombin III solution R4* to each well and shake the microplate but do not allow bubbles to form. Add 40 µL of *bovine factor Xa solution R1* to each well. Exactly 2 min after the addition of the factor Xa solution, add 80 µL of *chromogenic substrate R5*. Measure the absorbance at 405 nm (2.2.25) using a suitable reading device, exactly 4 min after the addition of the factor Xa solution. Measure the absorbance again at 405 nm (2.2.25), exactly 14 min after the addition of the factor Xa solution. Use ΔA ($A_{14} - A_4$) for the calculation of the anti-factor Xa activity. Determine the blank amidolytic activity in the same manner, using *tris(hydroxymethyl)aminomethane EDTA buffer solution pH 8.4 R* as the blank (minimum 8 blanks per microplate). Calculate the potency of the substance to be examined in units of anti-factor Xa activity per milligram using a suitable statistical method, for example the parallel-line assay (5.3).

STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states the number of units of anti-factor Xa activity per milligram.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dantrolene Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Skeletal muscle relaxant.

DEFINITION

Dantrolene Oral Suspension is a suspension of Dantrolene Sodium in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of dantrolene sodium, $C_{14}H_9N_4NaO_5,3½H_2O$

95.0 to 105.0% of the stated amount.

Shake the oral suspension vigorously before carrying out the following tests.

IDENTIFICATION

A. Shake a quantity of the oral suspension containing 0.1 g of Dantrolene Sodium with sufficient 0.01M *sodium hydroxide* to produce 100 mL, dilute 1 mL to 100 mL with 0.01M *sodium hydroxide*, filter and use the filtrate. The *light absorption*, Appendix II B, in the range 230 nm to 350 nm, of the final solution, exhibits a maximum at 314 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.5 to 5.5, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Related substances

www.webofpharma.com

https://nhathuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the oral suspension containing 50 mg of Dantrolene Sodium in 20 mL of *tetrahydrofuran* and 2 mL of *glacial acetic acid* and dilute with sufficient *absolute ethanol* to produce 100 mL.

(2) Dilute 1 mL of solution (1) to 100 mL with *absolute ethanol*.

(3) Dissolve 5 mg of *dantrolene sodium BPCRS* and 0.1 g of *theophylline BPCRS* in 20 mL of *tetrahydrofuran* and 2 mL of *glacial acetic acid* and dilute with sufficient *absolute ethanol* to produce 100 mL. Dilute 10 mL of the resulting solution to 100 mL with *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Zorbax Sil is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Adjust the flow rate of the mobile phase so that the retention time of the peak corresponding to dantrolene sodium is about 8 minutes.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 300 nm.

(f) Inject 10 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for at least twice the retention time of the principal peak.

MOBILE PHASE

9 volumes of *absolute ethanol*, 10 volumes of *glacial acetic acid* and 90 volumes of *hexane*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to theophylline and dantrolene is at least 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the total area of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of *dimethylformamide* to a weighed quantity of the oral suspension containing 60 mg of Dantrolene Sodium and dilute 1 volume of this solution to 100 volumes with the mobile phase.

(2) Dilute 1 volume of a 0.12% w/v solution of *dantrolene sodium BPCRS* in *dimethylformamide* to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with spherical particles of silica, 5 µm in diameter, the surface of which has been modified with chemically-bonded nitrile groups (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 262 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile* and 85 volumes of a phosphate buffer pH 6.8 prepared by dissolving 11.88 g of *disodium hydrogen orthophosphate* and 9.08 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{14}H_9N_4NaO_5,3½H_2O$, weight in volume, using the declared content of $C_{14}H_9N_4NaO_5$ in *dantrolene sodium BPCRS*. Each mg of $C_{14}H_9N_4NaO_5$ is equivalent to 1.1873 mg of $C_{14}H_9N_4NaO_5,3½H_2O$.

STORAGE

Dantrolene Oral Suspension should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

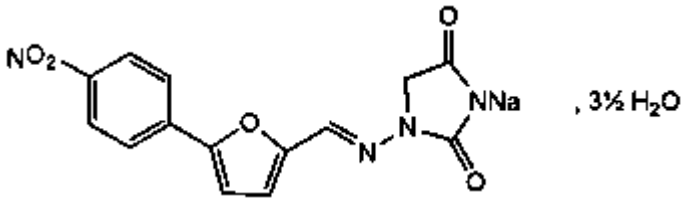
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dantrolene Sodium

General Notices



$C_{14}H_9N_4NaO_5,3½H_2O$ 399.3 *24868-20-0*

Action and use

Skeletal muscle relaxant.

Preparation

Dantrolene Oral Suspension

DEFINITION

Dantrolene Sodium is 1-(5-*p*-nitrophenylfurfurylideneamino)hydantoin sodium. It contains not less than 98.0% and not more than 102.0% of $C_{14}H_9N_4NaO_5$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A yellowish-orange to orange crystalline powder.

Very slightly soluble in *water*; slightly soluble in *ethanol (96%)*; sparingly soluble in *methanol*; practically insoluble in *acetone*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of dantrolene sodium (*RS 422*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. To 0.1 g of the substance being examined add 20 mL of *water* and 2 drops of *acetic acid*, shake well and filter. The filtrate yields the reactions characteristic of *sodium salts*, Appendix VI.

TESTS

Alkalinity

www.webofpharma.com

https://thuocngocanh.com/

Shake 0.7 g in 10 mL of *water* for 5 minutes and centrifuge. To 5 mL of the supernatant add 45 mL of *water* and 3 drops of *phenolphthalein solution R1* and 0.1 mL of *0.1M hydrochloric acid VS*. A red colour is not produced.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve 50 mg of the substance being examined in 20 mL of *tetrahydrofuran* and 2 mL of *glacial acetic acid* and dilute with sufficient *absolute ethanol* to produce 100 mL.

(2) Dilute 1 mL of solution (1) to 100 mL with *absolute ethanol*.

(3) Dissolve 5 mg of *dantrolene sodium BPCRS* and 0.1 g of *theophylline BPCRS* in 20 mL of *tetrahydrofuran* and 2 mL of *glacial acetic acid* and dilute with sufficient *absolute ethanol* to produce 100 mL. Further dilute 10 mL of this solution to 100 mL with *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Zorbax Sil is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Adjust the flow rate of the mobile phase so that the retention time of the peak corresponding to Dantrolene Sodium is about 8 minutes.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 300 nm.

(f) Inject 10 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for at least twice the retention time of the principal peak.

MOBILE PHASE

9 volumes of *absolute ethanol*, 10 volumes of *glacial acetic acid* and 90 volumes of *hexane*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to theophylline and dantrolene is at least 6.

LIMITS

In the chromatogram obtained with solution (1):

the total area of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Water

14.5 to 17.0% w/w, Appendix IX C. Use 0.2 g

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve 60 mg of the substance being examined in 50 mL of *dimethylformamide* and dilute 1 volume of the resulting solution to 100 volumes with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of a 0.12% w/v solution of *dantrolene sodium BPCRS* in *dimethylformamide* to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with spherical particles of silica, 5 µm in diameter, the surface of which has been modified with chemically-bonded nitrile groups (Spherisorb CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 262 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile* and 85 volumes of a phosphate buffer pH 6.8 prepared by dissolving 11.88 g of *disodium hydrogen orthophosphate* and 9.08 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_9N_4NaO_5$ in the substance being examined using the declared content of $C_{14}H_9N_4NaO_5$ in *dantrolene sodium BPCRS*.

© Crown Copyright 2022

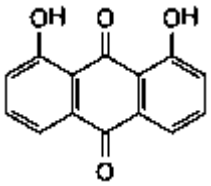
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dantron

General Notices



$C_{14}H_8O_4$ 240.2 *117-10-2*

Action and use

Anthraquinone stimulant laxative.

Preparation

Co-danthrusate Capsules

DEFINITION

Dantron is mainly 1,8-dihydroxyanthraquinone. It contains not less than 98.0% and not more than 102.0% of total phenols, calculated as $C_{14}H_8O_4$ and with reference to the dried substance.

CHARACTERISTICS

An orange, crystalline powder.

Practically insoluble in *water*; slightly soluble in *ether*; very slightly soluble in *ethanol (96%)*. It dissolves in solutions of alkali hydroxides.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of dantron *(RS 083)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.001% w/v solution in *dichloromethane* exhibits maxima at 255 nm and 285 nm and a less well-defined maximum at 275 nm. The *absorbance* at the maximum at 255 nm is about 0.82 and at the maximum at 285 nm is about 0.48, each calculated with reference to the dried substance.

C. Dissolve 5 mg in 5 mL of 1M *sodium hydroxide*. A clear red solution is produced immediately.

TESTS

Mercury

www.webofpharma.com

https://thuocngocanh.com/

To 0.50 g in a Kjeldahl flask add 2.5 mL of *nitric acid* and allow to stand until the initial vigorous reaction has subsided. Add 2.5 mL of *sulfuric acid* and heat until dense white fumes are evolved. Cool, add 2.5 mL of *nitric acid* and heat until fumes are again evolved. Repeat the procedure with a further 2.5 mL of *nitric acid*, cool, add 50 mL of *water*, boil the solution until the volume has been reduced to about 25 mL and cool. Transfer to a separating funnel using *water*, dilute to about 50 mL with *water* and add 50 mL of 0.5M *sulfuric acid*. Add 100 mL of *water*, 2 g of *hydroxylamine hydrochloride*, 1 mL of 0.05M *disodium edetate*, 1 mL of *glacial acetic acid* and 5 mL of *dichloromethane*, shake, allow to separate and discard the dichloromethane layer. Titrate the aqueous layer with a 0.0008% w/v solution of *dithizone* in *dichloromethane*, shaking vigorously after each addition, allowing the layers to separate and discarding the dichloromethane layer, until the dichloromethane layer remains green. Repeat the operation using a solution prepared by diluting 1 mL of *mercury standard solution (5 ppm Hg)* to 100 mL with 0.5M *sulfuric acid* and beginning at the words 'Add 100 mL of *water*…'. The volume of the dithizone solution required by the substance being examined does not exceed that required by the mercury standard solution.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve 50 mg of the substance being examined in 20 mL of *tetrahydrofuran* and dilute to 100 mL with the mobile phase.
(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase.
(3) Dissolve 50 mg of *dantron impurity standard BPCRS* in 20 mL of *tetrahydrofuran* and dilute to 100 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use an isocratic system using the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 1.5 times the retention time of the principal peak.

MOBILE PHASE

A mixture of 2.5 volumes of *glacial acetic acid*, 40 volumes of *tetrahydrofuran* and 60 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

— — a peak due to 1-hydroxyanthraquinone appears immediately before the principal peak, as indicated in the reference chromatogram supplied with *dantron impurity standard BPCRS*;

— the height of the trough separating the two peaks is not greater than one third of the height of the peak due to 1-hydroxyanthraquinone.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

— the area of any peak corresponding to 1-hydroxyanthraquinone is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.3% taking into account the correction factor of the impurity);

— — the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

— disregard any peak with a retention time less than one third of that of the principal peak.

Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

ASSAY

Dissolve 0.2 g in 50 mL of *anhydrous pyridine* and carry out Method II for *non-aqueous titration*, Appendix VIII A, using 0.1M *tetrabutylammonium hydroxide VS* as titrant and determining the end point potentiometrically. Each mL of 0.1M *tetrabutylammonium hydroxide VS* is equivalent to 24.02 mg of total phenols, calculated as $C_{14}H_8O_4$.

© Crown Copyright 2022

www.webofpharma.com

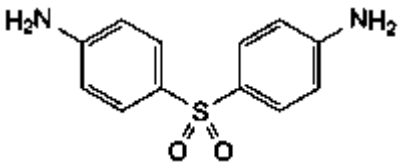
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dapsone

General Notices

(Ph. Eur. monograph 0077)



$C_{12}H_{12}N_2O_2S$ 248.3 *80-08-0*

Action and use

Folic acid synthesis inhibitor; treatment of leprosy.

Preparation

Dapsone Tablets

Ph Eur

DEFINITION

4,4′-Sulfonyldianiline.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish-white, crystalline powder.

Solubility

Pratically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute mineral acids.

It show polymorphism.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 175 °C to 181 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25.0 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*.

Spectral range 230-350 nm.

Absorption maxima 260 nm and 295 nm.

Specific absorbance at the absorption maxima:

— 260 nm: 700 to 760;

— 295 nm: 1150 to 1250.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *dapsone CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *ethyl acetate R*, *heptane R* (1:6:20:20 *V/V/V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 1 g/L solution of *4-dimethylaminocinnamaldehyde R* in a mixture of 1 volume of *hydrochloric acid R* and 99 volumes of *ethanol (96 per cent) R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 40.0 mg of the substance to be examined in 30 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2 mg of the substance to be examined, 2 mg of *4-(4-aminobenzene-1-sulfonyl)phenol R*, 2 mg of *4-(benzenesulfonyl)aniline R* and 2 mg of *4,4'-[oxybis[(4,1-phenylene)sulfonyl]]dianiline R* (impurity C) in the solvent mixture and dilute to 50 mL with the solvent mixture. Dilute 1 mL of the solution to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	75	25
10 - 20	75 → 50	25 → 50
20 - 35	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to dapsone (retention time = about 7 min): impurity A = about 1.1; impurity B = about 2.5; impurity C = about 3.5.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to dapsone and impurity A.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.9; impurity B = 2.7; impurity C = 1.7;

— for each impurity, use the concentration of dapsone in reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurity B*: maximum 0.4 per cent;

— *impurities A, C*: for each impurity, maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Carry out the determination of primary aromatic amino-nitrogen (2.5.8), using 0.100 g.

1 mL of *0.1 M sodium nitrite* is equivalent to 12.42 mg of $C_{12}H_{12}N_2O_2S$.

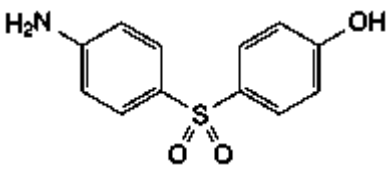
STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B, C.

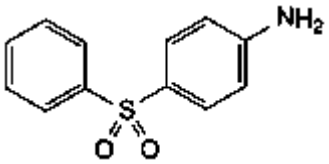
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, E, F.



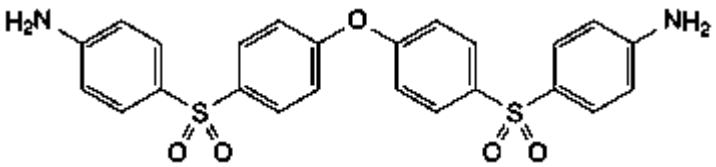
A. 4-(4-aminobenzene-1-sulfonyl)phenol,

www.webofpharma.com

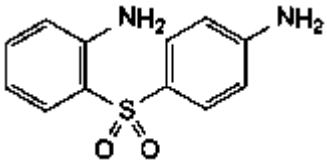
https://thuocngocanh.com/



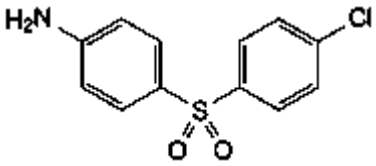
B. 4-(benzenesulfonyl)aniline,



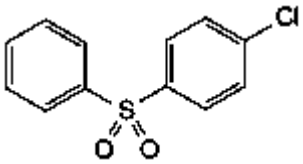
C. $1^4,7^4$-diamino-$2\lambda^6,6\lambda^6$-4-oxa-2,6-dithia-1,7(1),3,5(1,4)-tetrabenzenaheptaphane-2,2,6,6-tetrone,



D. 2-(4-aminobenzene-1-sulfonyl)aniline,



E. 4-(4-chlorobenzene-1-sulfonyl)aniline,



F. 1-(benzenesulfonyl)-4-chlorobenzene.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dapsone Tablets

General Notices

Action and use

Folic acid synthesis inhibitor; treatment of leprosy.

DEFINITION

Dapsone Tablets contain Dapsone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dapsone, $C_{12}H_{12}N_2O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of Dapsone with 20 mL of *acetone*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dapsone *(RS 084)*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) is similar in position, colour and size to that in the chromatogram obtained with solution (5).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 20 mL sample of the medium. To a volume of the filtered sample expected to contain 0.1 mg of Dapsone add 1 mL of a freshly prepared 0.5% w/v solution of *sodium nitrite*, and allow to stand for 3 minutes. Add 1.5 mL of a 1% w/v solution of *sulfamic acid*, allow to stand for 3 minutes, add 2.5 mL of a freshly prepared 0.2% w/v solution of N-*(1-naphthyl)-ethylenediamine dihydrochloride* in 0.1M *hydrochloric acid* and dilute to 20 mL with 1M *hydrochloric acid* (solution A). Carry out the procedure at the same time and in the same manner using a volume of 0.1M *hydrochloric acid* equal to that of the filtered sample and beginning at the words ‘add

www.webofpharma.com

https://thuocngocanh.com/

1 mL of a freshly prepared 0.5% w/v solution of *sodium nitrite*...' (solution B). Allow solutions A and B to stand for at least 2 minutes and measure the *absorbance* of solution A at the maximum at 538 nm, Appendix II B, using solution B in the reference cell.

(2) Repeat the operation using a solution containing 0.1 mg of *dapsone BPCRS* in a volume of 0.1M *hydrochloric acid* equal to that of the filtered sample and beginning at the words 'add 1 mL of a freshly prepared 0.5% w/v solution of *sodium nitrite* ...' and using solution B in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of dapsone, $C_{12}H_{12}N_2O_2S$, in the medium from the absorbances obtained and using the declared content of $C_{12}H_{12}N_2O_2S$ in *dapsone BPCRS*.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Dapsone with 10 mL of *methanol* and filter.
(2) Dilute 1 volume of solution (1) to 10 volumes with *methanol*.
(3) Dilute 1 volume of solution (2) to 10 volumes with *methanol*.
(4) Dilute 1 volume of solution (3) to 5 volumes with *methanol*.
(5) 0.1% w/v of *dapsone BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel G plate*.
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each of solutions (1), (3) and (4) and 1 µL of each of solutions (2) and (5).
(d) Develop the plate to 15 cm in an unsaturated tank.
(e) After removal of the plate, dry in air, spray with a 0.1% w/v solution of *4-dimethylaminocinnamaldehyde* in a mixture of 1 volume of *hydrochloric acid* and 99 volumes of *ethanol (96%)* and examine in daylight.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 6 volumes of *methanol*, 20 volumes of *ethyl acetate* and 20 volumes of n-*heptane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense that the spot in the chromatogram obtained with solution (3) (1%) and not more than two such spots are more intense than the spot in the chromatogram obtained with solution (4) (0.2%).

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.25 g of Dapsone in a mixture of 15 mL of *water* and 15 mL of 2M *hydrochloric acid*, add 3 g of *potassium bromide*, cool in ice and titrate slowly with 0.1M *sodium nitrite VS*, stirring constantly and determining the end point electrometrically. Each mL of 0.1M *sodium nitrite VS* is equivalent to 12.42 mg of $C_{12}H_{12}N_2O_2S$.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

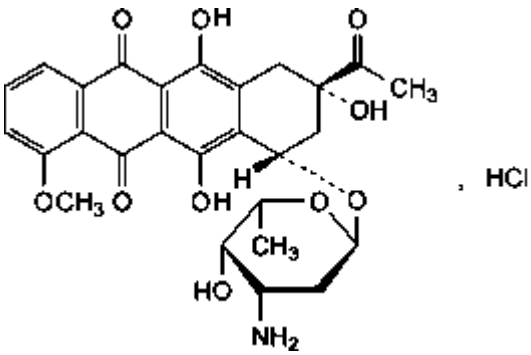
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Daunorubicin Hydrochloride

General Notices

(Ph. Eur. monograph 0662)



$C_{27}H_{30}ClNO_{10}$ 564.0 *23541-50-6*

Action and use

Cytostatic; anthracycline antibacterial.

Ph Eur

DEFINITION

(8*S*,10*S*)-8-Acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride.

Substance produced by certain strains of *Streptomyces coeruleorubidus* or *Streptomyces peucetius*.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is produced by methods of manufacture designed to eliminate or minimise the presence of histamine.

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

Crystalline, orange-red powder, hygroscopic.

Solubility

Freely soluble in water and in methanol, slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison daunorubicin hydrochloride CRS.

B. Dissolve about 10 mg in 0.5 mL of nitric acid R, add 0.5 mL of water R and heat over a flame for 2 min. Allow to cool and add 0.5 mL of silver nitrate solution R1. A white precipitate is formed.

TESTS

pH (2.2.3)

4.5 to 6.5.

Dissolve 50 mg in carbon dioxide-free water R and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of daunorubicin for system suitability CRS (containing impurities A, B and D) in 1 mL of mobile phase.

Reference solution (c) Dissolve 50.0 mg of daunorubicin hydrochloride CRS in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 25 °C.

Mobile phase Mix 43 volumes of acetonitrile R and 57 volumes of a solution containing 2.25 g/L of phosphoric acid R and 2.88 g/L of sodium laurilsulfate R.

Flow rate 1.0 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 254 nm.

Injection 5 µL of the test solution and reference solutions (a) and (b).

Run time 2.5 times the retention time of daunorubicin.

Identification of impurities Use the chromatogram supplied with *daunorubicin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and D.

Relative retention With reference to daunorubicin (retention time = about 27 min): impurity A = about 0.3; impurity D = about 0.5; impurity B = about 0.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurities D and B.

Calculation of percentage contents:

— for each impurity, use the concentration of daunorubicin hydrochloride in reference solution (a).

Limits:

— *impurity B*: maximum 1.0 per cent;

— *impurities A, D*: for each impurity, maximum 0.5 per cent;

— *any other impurity*: for each impurity, maximum 0.5 per cent;

— *total (excluding impurities A, B and D)*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent.

Butanol (*2.4.24, System B*)

Maximum 1.0 per cent.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.100 g.

Bacterial endotoxins (*2.6.14*)

Less than 4.3 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

www.webofpharma.com

https://thuocngocanh.com/

Calculate the percentage content of $C_{27}H_{30}ClNO_{10}$ taking into account the assigned content of *daunorubicin hydrochloride CRS*.

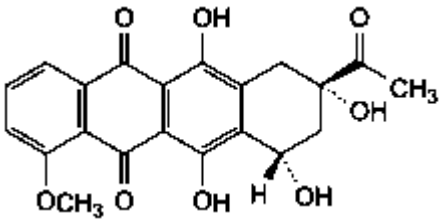
STORAGE

In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

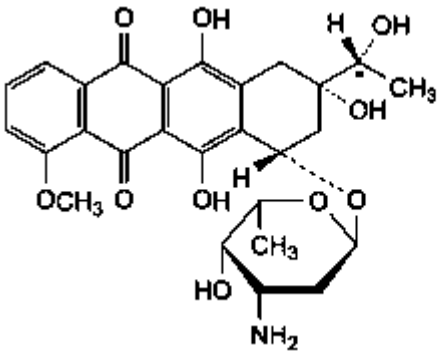
IMPURITIES

Specified impurities *A, B, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, F, G.*

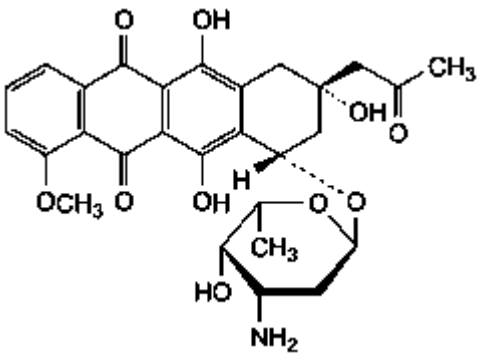


A. (8*S*,10*S*)-8-acetyl-6,8,10,11-tetrahydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (daunorubicin aglycone, daunorubicinone),



and epimer at C*

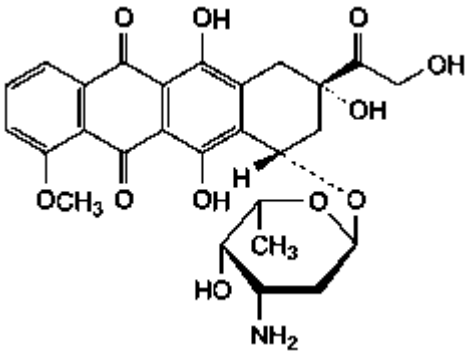
B. (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-[(1*RS*)-1-hydroxyethyl]-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (daunorubicinol),



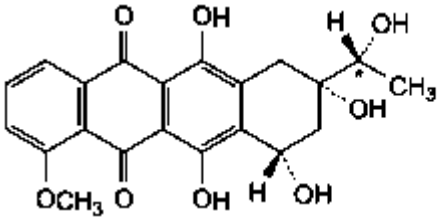
www.webofpharma.com

https://thuocngocanh.com/

C. (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-8-(2-oxopropyl)-7,8,9,10-tetrahydrotetracene-5,12-dione (feudomycin B),

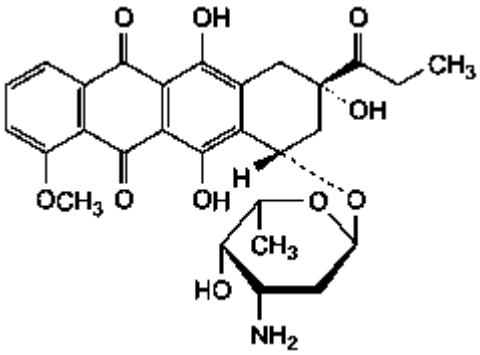


D. (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (doxorubicin),

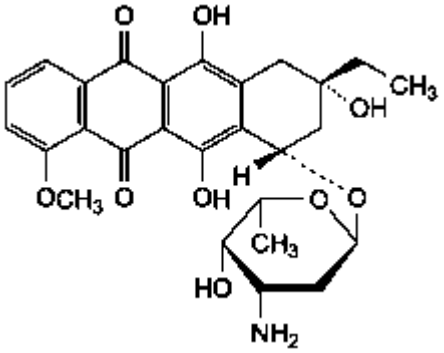


and epimer at C*

E. (8*S*,10*S*)-6,8,10,11-tetrahydroxy-8-[(1*RS*)-1-hydroxyethyl]-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (daunorubicinol aglycone),



F. (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-8-propanoyl-7,8,9,10-tetrahydrotetracene-5,12-dione (14-methyldaunorubicin),



www.webofpharma.com

https://thuocngocanh.com/

G. (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-ethyl-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (feudomycin A).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Decyl Oleate

General Notices

(Ph. Eur. monograph 1307)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture consisting of decyl esters of fatty acids, mainly oleic (*cis*-9-octadecenoic) acid.

A suitable antioxidant may be added.

CHARACTERS

Appearance

Clear, pale yellow or colourless liquid.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent), with methylene chloride and with light petroleum (bp: 40-60 °C).

IDENTIFICATION

A. Relative density (see Tests).

B. Saponification value (see Tests).

C. Oleic acid (see Tests).

TESTS

Relative density (*2.2.5*)

0.860 to 0.870.

Acid value (*2.5.1*)

Maximum 1.0, determined on 10.0 g.

Iodine value (*2.5.4, Method A*)

www.webofpharma.com

https://thietbiluocngocanh.com/

55 to 70.

Peroxide value (*2.5.5, Method A*)

Maximum 10.0.

Saponification value (*2.5.6*)

130 to 140, determined on 2.0 g.

Oleic acid (*2.4.22, Method A*)

Minimum 60.0 per cent in the fatty acid fraction of the substance.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g.

Total ash (*2.4.16*)

Maximum 0.1 per cent, determined on 2.0 g.

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

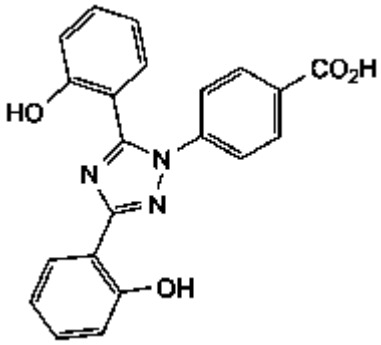
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Deferasirox

General Notices

(Ph. Eur. monograph 2933)



$C_{21}H_{15}N_3O_4$ 373.4 *201530-41-8*

Action and use

Selective iron(III) chelator; treatment of iron overload

Preparation

Deferasirox Dispersible Tablets

Ph Eur

DEFINITION

4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow powder.

Solubility

Practically insoluble in water, very soluble in dimethyl sulfoxide, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison deferasirox CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Use only colourless glassware. Store the solutions at 2-8 °C.*

Buffer solution 0.100 g/L solution of sodium edetate R adjusted to pH 2.1 with phosphoric acid R.

Solvent mixture 0.040 g/L solution of sodium edetate R, acetonitrile R (25:75 *V/V*).

Test solution (a) Dissolve 30.0 mg of the substance to be examined in 15 mL of the solvent mixture with vigorous shaking (this may take up to 20 min) and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of deferasirox CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of deferasirox for system suitability CRS (containing impurity D) in 8 mL of the solvent mixture with vigorous shaking and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 3.0 mg of deferasirox impurity B CRS in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 100.0 mL with the solvent mixture. Dilute 3.0 mL of this solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R (3.5 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, buffer solution, water for chromatography R (10:10:80 *V/V/V*);

— *mobile phase B*: buffer solution, acetonitrile R (10:90 *V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	62	38
10 - 14	62 → 0	38 → 100
14 - 16	0	100

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 250 nm.

Autosampler Set at 5 °C.

Injection 5 µL of test solution (a) and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *deferasirox for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity B.

Relative retention With reference to deferasirox (retention time = about 10 min): impurity B = about 0.5; impurity D = about 0.95.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity D and deferasirox in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— for each impurity, use the concentration of deferasirox in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent.

Impurity F

Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

Solvent mixture *phosphoric acid R*, *water R*, *acetone R* (25:100:900 *V/V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 0.600 g of the substance to be examined in 1 mL of *dimethyl sulfoxide R*, add 2 mL of the solvent mixture and mix thoroughly using a vortex mixer. Heat the solution at 45 °C for 35 min, then cool to 2-8 °C for 1 h. Dilute to 5.0 mL with mobile phase A, previously cooled to 2-8 °C. Shake vigorously using a mechanical shaker for 2 min. Centrifuge immediately at 4000 *g* for 5 min and filter the supernatant through a membrane filter (nominal pore size 0.45 µm). If a precipitation is still observed, allow to stand for 1 h at 2-8 °C. Filter again through a membrane filter (nominal pore size 0.45 µm) immediately before injection.

Reference solution (a) Dissolve 6.0 mg of *deferasirox impurity F CRS* in 1 mL of *dimethyl sulfoxide R* and dilute to 20.0 mL with *water R*. Dilute 1.0 mL of the solution to 10.0 mL with *dimethyl sulfoxide R*.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *dimethyl sulfoxide R*. To 1.0 mL of this solution add 5 mL of *dimethyl sulfoxide R* and 20 mL of the solvent mixture. Heat this solution at 45 °C for 35 min, cool to 2-8 °C and dilute to 50.0 mL with mobile phase A, previously cooled to 2-8 °C.

Reference solution (c) To 2.0 mL of reference solution (b) add 1 mL of *dimethyl sulfoxide R* and 4 mL of the solvent mixture and dilute to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *acetonitrile R*, *water for chromatography R* (2:100:900 *V/V/V*);

— *mobile phase B*: *phosphoric acid R*, *water for chromatography R*, *acetonitrile R* (2:100:900 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 8	90 → 58	10 → 42
8 - 8.1	58 → 0	42 → 100
8.1 - 16	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 316 nm.

Injection 25 µL of the test solution and reference solutions (b) and (c).

Relative retention With reference to deferasirox (retention time = about 10 min): impurity F acetone derivative = about 0.5.

www.webofpharma.com

https://thuocngocanh.com/

System suitability:

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity F acetone derivative in the chromatogram obtained with reference solution (c);

— *repeatability*: maximum relative standard deviation of 5.0 per cent for the peak due to impurity F acetone derivative determined on 6 injections of reference solution (b).

Calculation of percentage content:

— for impurity F, use the concentration of impurity F in reference solution (b).

Limit:

— *impurity F*: maximum 0.5 ppm.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

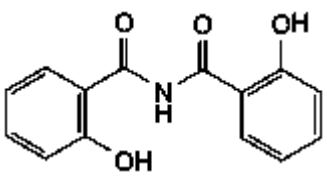
Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{21}H_{15}N_3O_4$ taking into account the assigned content of *deferasirox CRS*.

IMPURITIES

Specified impurities *F*.

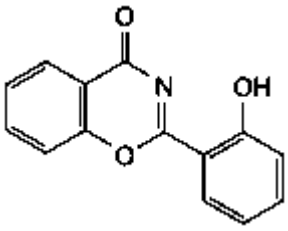
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E*.



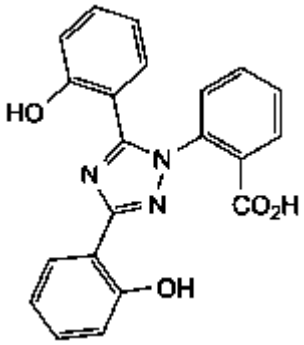
A. 2-hydroxy-*N*-(2-hydroxybenzoyl)benzamide,

www.webofpharma.com

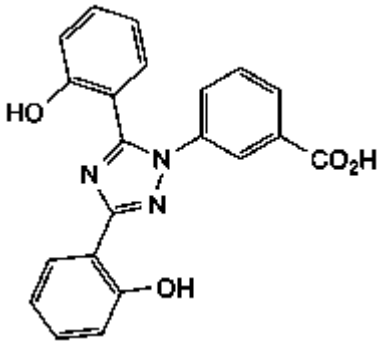
https://thuocngocanh.com/



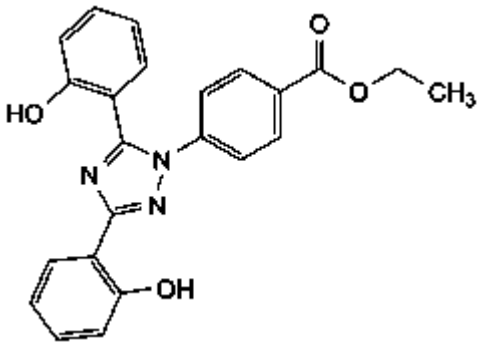
B. 2-(2-hydroxyphenyl)-4*H*-1,3-benzoxazin-4-one,



C. 2-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid,



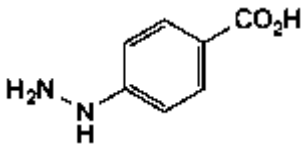
D. 3-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid,



E. ethyl 4-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoate,

www.webofpharma.com

https://thuvienthuocngocanh.com/



F. 4-hydrazinylbenzoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Deferasirox Dispersible Tablets

General Notices

(Ph. Eur. monograph 2934)

Action and use

Selective iron(III) chelator; treatment of iron overload.

Ph Eur

DEFINITION

Dispersible tablets containing *Deferasirox (2933)*, for human use.

They comply with the monograph Tablets (0478) and with the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of deferasirox ($C_{21}H_{15}N_3O_4$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 200-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Use only colourless glassware.*

Buffer solution A 0.100 g/L solution of *sodium edetate R* adjusted to pH 2.1 with *phosphoric acid R*.

Solvent mixture *acetonitrile R*, *water R*, *tetrahydrofuran R* (30:30:40 *V/V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution *Prepare as rapidly as possible*. Crush 20 tablets to obtain a homogeneous powder. Accurately weigh a quantity of the powder containing the equivalent of 500 mg of deferasirox. Add 250.0 mL of the solvent mixture. Stir for about 5 min and sonicate for about 10 min. Filter the solution and dilute 2.0 mL of the filtrate to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 4 mg of *deferasirox for system suitability CRS* (containing impurity D) in 20 mL of the solvent mixture and dilute to 25 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R* (3.5 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, buffer solution, *water for chromatography R* (10:10:80 *V/V/V*);

— *mobile phase B*: buffer solution, *acetonitrile R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	65	35
2 - 10	65 → 60	35 → 40
10 - 15	60 → 20	40 → 80
15 - 16	20	80

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *deferasirox for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to deferasirox (retention time = about 12 min): impurity D = about 0.95.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity D and deferasirox.

www.webofpharma.com

https://thuocngocanh.com/

Calculation of percentage contents:

— for each impurity, use the concentration of deferasirox in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium Mix 112 mL of an 8.4 g/L solution of *sodium hydroxide R* and 250 mL of a 27.2 g/L solution of *potassium dihydrogen phosphate R* and dilute to 1000 mL with *water R*. Adjust to pH 6.8 if necessary, using an 8.4 g/L solution of *sodium hydroxide R* or a 27.2 g/L solution of *potassium dihydrogen phosphate R*. Add 5 g of *polysorbate 20 R* and mix. Use 900 mL of the medium.

Rotation speed 50 r/min.

Time 30 min.

Analysis Ultraviolet and visible absorption spectrophotometry (*2.2.25*), using a path length of 1 mm.

Test solutions Samples withdrawn from the dissolution vessel and filtered. Mix 1 volume of the clear filtrate and 1 volume of *acetonitrile R*.

When a different path length is used, the solutions may be diluted accordingly (e.g. for a path length of 1 cm, 10-fold dilution for 125 mg, 250 mg and 500 mg tablets).

Measure the absorbance of the solutions at 285 nm.

Calculate the amount of dissolved deferasirox ($C_{21}H_{15}N_3O_4$), expressed as a percentage of the content stated on the label, taking the specific absorbance to be 365.

Acceptance criterion:

— *Q* = 75 per cent after 30 min.

ASSAY

Liquid chromatography (*2.2.29*).

Buffer solution A 0.100 g/L solution of *sodium edetate R* adjusted to pH 2.1 with *phosphoric acid R*.

Solvent mixture *acetonitrile R*, *water R*, *tetrahydrofuran R* (30:30:40 *V/V/V*).

Test solution. Prepare as rapidly as possible Crush 20 tablets to obtain a homogeneous powder. Accurately weigh a quantity of the powder containing the equivalent of 500 mg of deferasirox. Add 250.0 mL of the solvent mixture. Stir for about 5 min and sonicate for about 10 min. Filter the solution and dilute 2.0 mL of the filtrate to 25.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution Dissolve 16.0 mg of *deferasirox CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R* (3.5 µm);

— *temperature*: 30 °C.

Mobile phase Buffer solution, *water for chromatography R*, *acetonitrile R* (10:40:50 *V/V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

Run time Twice the retention time of deferasirox (retention time = about 1.8 min).

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

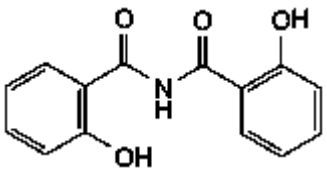
Calculate the percentage content of deferasirox ($C_{21}H_{15}N_3O_4$) taking into account the assigned content of *deferasirox CRS*.

STORAGE

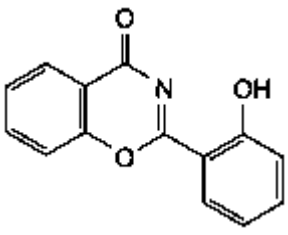
Protected from moisture.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, B, C, D, E.*



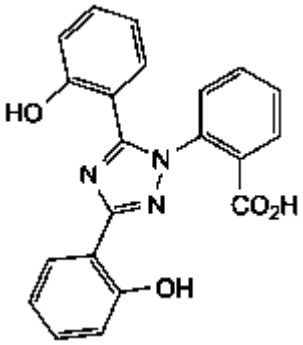
A. 2-hydroxy-*N*-(2-hydroxybenzoyl)benzamide,



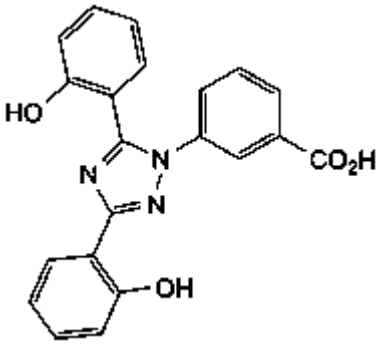
www.webofpharma.com

https://nhathuocngocanh.com/

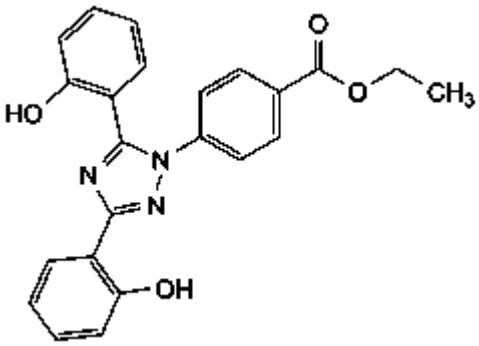
B. 2-(2-hydroxyphenyl)-4*H*-1,3-benzoxazin-4-one,



C. 2-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid,



D. 3-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid,



E. ethyl 4-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoate.

Ph Eur

[1] The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

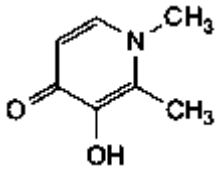
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Deferiprone

General Notices

(Ph. Eur. monograph 2236)



$C_7H_9NO_2$ 139.2 *30652-11-0*

Action and use

Chelating agent (iron).

Preparations

Deferiprone Oral Solution

Deferiprone Tablets

Ph Eur

DEFINITION

3-Hydroxy-1,2-dimethylpyridin-4-(1*H*)-one.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pinkish-white powder.

Solubility

Sparingly soluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison deferiprone CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Use only colourless glassware. Protect the solutions from light.*

Solution A Dissolve 2.91 g of sodium edetate R, 4.01 g of sodium octanesulfonate monohydrate R and 6.20 g of dipotassium hydrogen phosphate R in water for chromatography R and dilute to 2000 mL with the same solvent; adjust to pH 3.0 with phosphoric acid R.

Solution B Dissolve 0.73 g of sodium edetate R, 1.0 g of sodium octanesulfonate monohydrate R and 1.55 g of dipotassium hydrogen phosphate R in water for chromatography R and dilute to 2000 mL with the same solvent; adjust to pH 3.0 with phosphoric acid R.

Solvent mixture acetonitrile R, water R (10:90 *V/V*).

Test solution (a) Dissolve 0.100 g of the substance to be examined in a volume of the mobile phase corresponding to about 2/3 of the final volume and dilute to 100.0 mL with the mobile phase.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in a volume of the solvent mixture corresponding to about 2/3 of the final volume and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 200.0 mL with the mobile phase described under Assay.

Reference solution (a) Dissolve 2 mg of maltol R (impurity B) in the mobile phase and dilute to 100.0 mL with the mobile phase. To 2.5 mL of the solution add 10 mL of test solution (a) and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 50.0 mg of deferiprone CRS in a volume of the solvent mixture corresponding to about 2/3 of the final volume and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 200.0 mL with the mobile phase described under Assay.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: styrene-divinylbenzene copolymer R (5 µm);

— *temperature*: 30 °C.

Mobile phase acetonitrile R, solution A (10:90 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Preconditioning of the column Rinse for 20 min with the mobile phase before each series of injections.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 3.5 times the retention time of deferiprone.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to deferiprone (retention time = about 12 min): impurity B = about 0.5.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity B and deferiprone.

Calculation of percentage contents:

— for each impurity, use the concentration of deferiprone in reference solution (b).

Limits:

— *impurity B*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent.

Water (2.5.32)

Maximum 0.5 per cent, determined on 0.100 g by direct sample introduction.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase *acetonitrile R*, solution B (10:90 *V/V*).

Injection 10 µL of test solution (b) and reference solution (c).

Run time Twice the retention time of deferiprone.

Retention time Deferiprone = about 7.7 min.

www.webofpharma.com

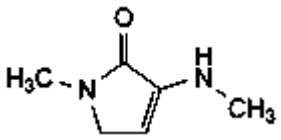
https://thuocngocanh.com/

Calculate the percentage content of $C_7H_9NO_2$ taking into account the assigned content of *deferiprone CRS*.

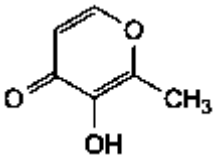
IMPURITIES

Specified impurities B.

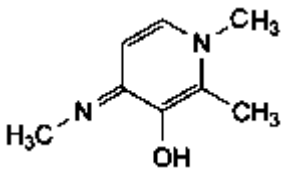
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C.



A. 1-methyl-3-(methylamino)-1,5-dihydro-2*H*-pyrrol-2-one,



B. 3-hydroxy-2-methyl-4*H*-pyran-4-one (maltol),



C. 1,2-dimethyl-4-[(Ξ)-methylimino]-1,4-dihydropyridin-3-ol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Deferiprone Oral Solution

General Notices

(Ph. Eur. monograph 2987)

Action and use

Chelating agent (iron).

Ph Eur

DEFINITION

Oral solution of *Deferiprone (2236)*, for human use.

It complies with the monograph Liquid preparations for oral use (0672) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of deferiprone ($C_7H_9NO_2$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with test solution (b) is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (c).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Use only colourless glassware. Protect the solutions from light.*

Buffer solution Dissolve 0.25 g of *sodium edetate R*, 4.3 g of *sodium octanesulfonate monohydrate R* and 13.8 g of *sodium dihydrogen phosphate monohydrate R* in *water for chromatography R*, and dilute to 1000 mL with the same solvent; adjust to pH 2.1 with *phosphoric acid R*.

www.webofpharma.com

https://thuocngocanh.com/

Solvent mixture methanol R, buffer solution (20:80 *V/V*)

Test solution (a) To a volume of the preparation to be examined containing the equivalent of 100 mg of deferiprone, add the mobile phase and dilute to 100.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (b) to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of maltol R (impurity B) in the mobile phase and dilute to 100 mL with the mobile phase. Mix 2.5 mL of the solution and 10 mL of test solution (a) and dilute to 100 mL with the mobile phase.

Reference solution (c) Dissolve 50.0 mg of deferiprone CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase methanol R, buffer solution (13:87 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 4 times the retention time of deferiprone.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to deferiprone (retention time = about 11 min): impurity B = about 0.3.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity B and deferiprone.

Calculation of percentage contents:

— for each impurity, use the concentration of deferiprone in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *reporting threshold*: 0.05 per cent; disregard the peak due to impurity B.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Solvent mixture.

Flow rate 1.1 mL/min.

Injection Test solution (b) and reference solution (c).

Run time 1.5 times the retention time of deferiprone.

Retention time Deferiprone = about 7 min.

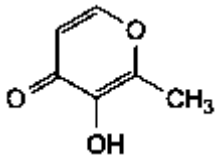
System suitability Reference solution (c):

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

Calculate the percentage content of deferiprone ($C_7H_9NO_2$) taking into account the assigned content of *deferiprone CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: B*.



B. 3-hydroxy-2-methyl-4*H*-pyran-4-one (maltol).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Deferiprone Tablets

General Notices

(Ph. Eur. monograph 2986)

Action and use

Chelating agent (iron).

Ph Eur

DEFINITION

Tablets containing *Deferiprone (2236)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of deferiprone ($C_7H_9NO_2$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with test solution (b) is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (c).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

TESTS

Related substances

Liquid chromatography (2.2.29). *Use only colourless glassware. Protect the solutions from light.*

Buffer solution Dissolve 2.91 g of *sodium edetate R*, 4.01 g of *sodium octanesulfonate monohydrate R* and 6.20 g of *dipotassium hydrogen phosphate R* in *water for chromatography R* and dilute to 2000 mL with the same solvent; adjust to pH 3.0 with *phosphoric acid R*.

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Crush 20 tablets to obtain a homogeneous powder. Dissolve an amount of the powder containing the equivalent of 100 mg of deferiprone in the mobile phase by sonicating for approximately 15 min and dilute to 100.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 200.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of test solution (b) to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *maltol R* (impurity B) in the mobile phase and dilute to 100 mL with the mobile phase. Mix 5 mL of the solution and 10 mL of test solution (a) and dilute to 100 mL with the mobile phase.

Reference solution (c) Dissolve 50.0 mg of *deferiprone CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 200.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, buffer solution (10:90 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Preconditioning of the column Rinse for 20 min with the mobile phase before each series of injections.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 3.5 times the retention time of deferiprone.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to deferiprone (retention time = about 12 min): impurity B = about 0.5.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity B and deferiprone.

Calculation of percentage contents:

— for each impurity, use the concentration of deferiprone in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *reporting threshold*: 0.05 per cent; disregard the peak due to impurity B.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium 10.3 g/L solution of *hydrochloric acid R*. Use 1000 mL of the medium.

Rotation speed 50 r/min.

Time 45 min.

Analysis Ultraviolet and visible absorption spectrophotometry (*2.2.25*), using a path length of 2 mm.

Test solutions Samples withdrawn from the dissolution vessel and filtered.

Reference solution Dissolve a suitable quantity of *deferiprone CRS* in a suitable volume of the dissolution medium to obtain a concentration of deferiprone corresponding to the theoretical concentration of deferiprone in the test solution, based on the labelled content of the tablets.

When a different path length is used, the solutions may be diluted accordingly (e.g. for a path length of 1 cm, 50-fold dilution for 500 mg tablets and 100-fold for 1000 mg tablets).

Measure the absorbance of the solutions at the absorption maximum at 275 nm, with a background correction at 490 nm.

Calculate the amount of dissolved deferiprone ($C_7H_9NO_2$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *deferiprone CRS*.

Acceptance criterion:

— *Q* = 80 per cent after 45 min.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection 10 µL of test solution (b) and reference solution (c).

Run time Twice the retention time of deferiprone.

System suitability Reference solution (c):

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

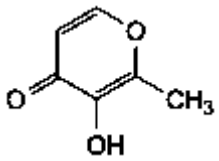
Calculate the percentage content of deferiprone ($C_7H_9NO_2$) taking into account the assigned content of *deferiprone CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: B.*

www.webofpharma.com

https://thuathuocngocanh.com/



B. 3-hydroxy-2-methyl-4*H*-pyran-4-one (maltol).

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Demeclocycline Capsules

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Demeclocycline Capsules contain Demeclocycline Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of demeclocycline hydrochloride, $C_{21}H_{21}ClN_2O_8,HCl$

90.0 to 107.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the contents of the capsules containing 10 mg of Demeclocycline Hydrochloride with 20 mL of *methanol* and centrifuge.

(2) 0.05% w/v of *demeclocycline hydrochloride BPCRS* in *methanol*.

(3) 0.05% w/v of each of *demeclocycline hydrochloride BPCRS*, *oxytetracycline hydrochloride BPCRS* and *metacycline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel H*. Adjust the pH of a 10% w/v solution of *disodium edetate* to 7.0 with 10M *sodium hydroxide* and spray the solution evenly onto the plate (about 10 mL for a plate 100 mm × 200 mm). Allow the plate to dry in a horizontal position for at least 1 hour. At the time of use, dry the plate in an oven at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µl of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in a stream of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Add 20 mL of warm *methanol* to a quantity of the contents of the capsules containing 10 mg of Demeclocycline Hydrochloride, allow to stand for 20 minutes, filter and evaporate the filtrate to dryness on a water bath. To 0.5 mg of the residue add 2 mL of *sulfuric acid*; a purple colour is produced. Add 1 mL of *water*; the colour changes to yellow.

C. To 1 mg of the residue obtained in test B add 7 mL of *water* and 7 mL of 2M *hydrochloric acid* and heat gently for 30 seconds. No colour is produced immediately.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 ml of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw a 10 ml sample of the medium and filter. Dilute the filtered solution, if necessary, with sufficient 0.1M *hydrochloric acid* to give a solution expected to contain about 0.015% w/v of Demeclocycline Hydrochloride.

(2) 0.015% w/v of *demeclocycline hydrochloride BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 ml per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 355 nm.

(f) Inject 20 µl of each solution.

MOBILE PHASE

20 volumes of *dimethylformamide* and 80 volumes of 0.1M *oxalic acid* the pH of which has been adjusted to 2.2 with *triethylamine*.

DETERMINATION OF CONTENT

Calculate the total content of demeclocycline hydrochloride, $C_{21}H_{21}ClN_2O_8$,HCl, in the medium using the declared content of $C_{21}H_{21}ClN_2O_8$,HCl in *demeclocycline hydrochloride BPCRS*.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the contents of the capsules containing 0.5 g of Demeclocycline Hydrochloride with 50 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 100 mL, filter and dilute 1 volume of the filtrate to 5 volumes with 0.01M *hydrochloric acid*.

(2) 0.010% w/v of *demeclocycline hydrochloride BPCRS* in 0.01M *hydrochloric acid*.

(3) 0.015% w/v of each of *demeclocycline hydrochloride BPCRS* and *4-epidemeclocycline hydrochloride EPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (10%);

the sum of the areas of all the *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (15%).

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, the contents of the capsules lose not more than 5.0% of their weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the mixed contents of 20 capsules containing 0.5 g of Demeclocycline Hydrochloride with 50 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 100 mL, filter and dilute 1 volume of the filtrate to 5 volumes with 0.01M *hydrochloric acid*.

(2) 0.10% w/v of *demeclocycline hydrochloride BPCRS* in 0.01M *hydrochloric acid*.

(3) 0.015% w/v of each of *demeclocycline hydrochloride BPCRS* and *4-epidemeclocycline hydrochloride EPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.0.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{21}ClN_2O_8$,HCl in the capsules using the declared content of $C_{21}H_{21}ClN_2O_8$,HCl in *demeclocycline hydrochloride BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

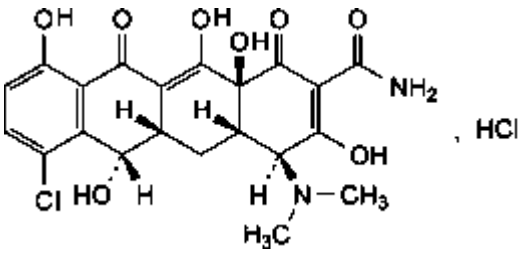
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Demeclocycline Hydrochloride

General Notices

(Ph. Eur. monograph 0176)



$C_{21}H_{22}Cl_2N_2O_8$ 501.3 *64-73-3*

Action and use

Tetracycline antibacterial.

Preparation

Demeclocycline Capsules

Ph Eur

DEFINITION

(4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-Chloro-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride.

Substance produced by certain strains of *Streptomyces aureofaciens*.

Content

89.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Yellow powder.

Solubility

https://thuocngocanh.com/

Solubility

Soluble or sparingly soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *demeclocycline hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *demeclocycline hydrochloride CRS*, 5 mg of *chlortetracycline hydrochloride R* and 5 mg of *tetracycline hydrochloride R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase Mix 20 volumes of *acetonitrile R*, 20 volumes of *methanol R* and 60 volumes of a 63 g/L solution of *oxalic acid R* previously adjusted to pH 2 with *concentrated ammonia R*.

Application 1 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability The chromatogram obtained with reference solution (b) shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

B. To about 2 mg add 5 mL of *sulfuric acid R*. A violet colour develops. Add the solution to 2.5 mL of *water R*. The colour becomes yellow.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

2.0 to 3.0.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Buffer 1 22.2 g/L solution of *sodium edetate R* adjusted to pH 7.5 with a 40 g/L solution of *sodium hydroxide R*.

www.webofpharma.com

https://thuocngocanh.com/

Buffer 2 17.0 g/L solution of *tetrapropylammonium hydrogen sulfate R* adjusted to pH 7.5 with a 40 g/L solution of *sodium hydroxide R*.

Test solution Dissolve 25.0 mg of the substance to be examined in a 1.0 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Reference solution (a) Dissolve 25.0 mg of *demeclocycline hydrochloride CRS* in a 1.0 g/L solution of *hydrochloric acid R* and dilute to 50.0 mL with the same solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a 1.0 g/L solution of *hydrochloric acid R*.

Reference solution (c) Dissolve 5 mg of *demeclocycline for system suitability CRS* (containing impurities A, B, C, E and G) in a 1.0 g/L solution of *hydrochloric acid R* and dilute to 10 mL with the same solution.

Column:

— *size*: *l* = 0.075 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography with embedded polar groups R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water for chromatography R*, buffer 1, buffer 2 (2:28:35:35 *V/V/V/V*);

— *mobile phase B*: *acetonitrile R*, buffer 1, buffer 2 (30:35:35 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	83	17
5 - 15	83 → 30	17 → 70
15 - 25	30	70

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *demeclocycline for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, E and G.

Relative retention With reference to demeclocycline (retention time = about 14 min): impurity C = about 0.3; impurity B = about 0.7; impurity A = about 0.8; impurity E = about 1.2; impurity G = about 1.6.

System suitability Reference solution (c):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 2.5 between the peaks due to impurities A and B.

Calculation of percentage contents:

— for each impurity, use the concentration of demeclocycline hydrochloride in reference solution (b).

Limits:

— *impurities A, B*: for each impurity, maximum 5.0 per cent;

— *impurities C, G*: for each impurity, maximum 0.3 per cent;

— *impurity E*: maximum 0.2 per cent;

— *any other impurity*: for each impurity, maximum 0.15 per cent;

— *total*: maximum 10.0 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 10 µL of the test solution and reference solution (a).

Calculate the percentage content of $C_{21}H_{22}Cl_2N_2O_8$ using the chromatogram obtained with reference solution (a) and taking into account the assigned content of *demeclocycline hydrochloride CRS*.

STORAGE

Protected from light.

IMPURITIES

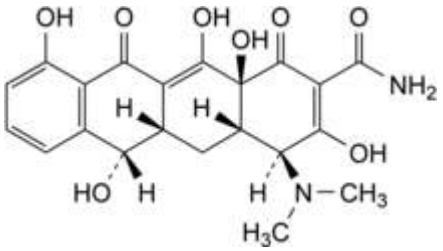
Specified impurities *A, B, C, E, G*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

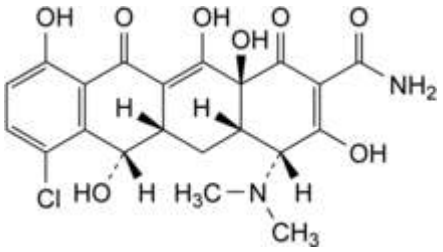
www.webofpharma.com

https://thuocngocanh.com/

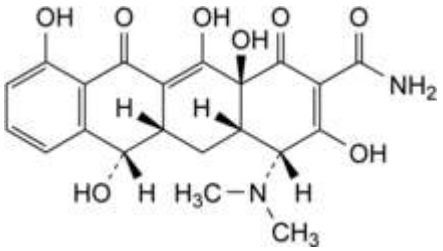
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, F.*



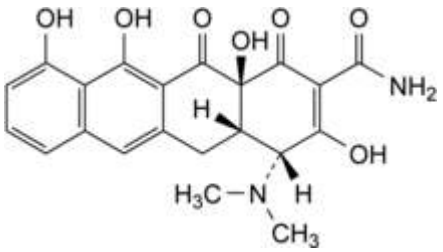
A. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (demethyltetracycline),



B. (4*R*,4a*S*,5a*S*,6*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epidemeclocycline),



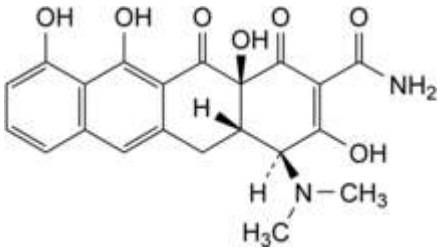
C. (4*R*,4a*S*,5a*S*,6*S*,12a*S*)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epidemethyltetracycline),



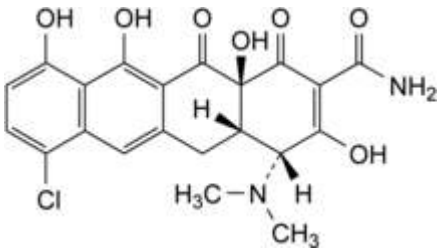
D. (4*R*,4a*S*,12a*S*)-4-(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (4-epianhydrodemethyltetracycline),

www.webofpharma.com

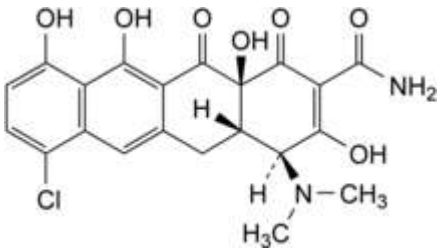
https://thuocngocanh.com/



E. (4*S*,4a*S*,12a*S*)-4-(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (anhydrodemethyltetracycline),



F. (4*R*,4a*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (4-epianhydrodemeclocycline),



G. (4*S*,4a*S*,12a*S*)-7-chloro-4-(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide (anhydrodemeclocycline).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dental-type Silica

General Notices

(Ph. Eur. monograph 1562)

Action and use

Excipient.

Ph Eur

DEFINITION

Amorphous silica (precipitated, gel or obtained by flame hydrolysis).

Content

94.0 per cent to 100.5 per cent of SiO_2 (ignited substance).

CHARACTERS

Appearance

White or almost white, light, fine, amorphous powder.

Solubility

Practically insoluble in water and in mineral acids. It dissolves in hydrofluoric acid and hot solutions of alkali hydroxides.

IDENTIFICATION

About 20 mg gives the reaction of silicates (*2.3.1*).

TESTS

Solution S

To 2.5 g add 50 mL of *hydrochloric acid R* and mix. Heat on a water-bath for 30 min, stirring from time to time. Evaporate to dryness. Add to the residue a mixture of 8 mL of *dilute hydrochloric acid R* and 24 mL of *water R*. Heat to boiling and filter under reduced pressure through a sintered-glass filter (16) (*2.1.2*). Wash the residue on the filter with a hot mixture of 3 mL of *dilute hydrochloric acid R* and 9 mL of *water R*. Wash with small quantities of *water R*, combine the washings and the filtrate, and dilute to 50 mL with *water R*.

pH (*2.2.3*)

www.webofpharma.com

https://thuocngocanh.com/

3.2 to 8.9.

Suspend 5 g in a mixture of 5 mL of a 7.46 g/L solution of *potassium chloride R* and 90 mL of *carbon dioxide-free water R*.

Chlorides

Liquid chromatography (*2.2.29*) as described in the test for sulfates.

Retention time Chlorides = about 4 min.

Limit:

— *chlorides*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.3 per cent).

Sulfates

Liquid chromatography (*2.2.29*).

Test solution To 0.625 g of the substance to be examined add 30 mL of *water R* and boil for 2 h. Allow to cool and quantitatively transfer to a 50 mL graduated flask. Dilute to 50.0 mL with *water R*. Dilute 5.0 mL of the supernatant to 50.0 mL with *water R* and filter through a membrane filter (nominal pore size 0.45 µm).

Reference solution Dissolve 0.50 g of *anhydrous sodium sulfate R* and 0.062 g of *sodium chloride R* in *water R* and dilute to 1000.0 mL with *water R*. Dilute 5.0 mL of the solution to 50.0 mL with *water R*.

Column:

— *material*: non-metallic;

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: suitable anion-exchange resin (30-50 µm).

Mobile phase Dissolve 0.508 g of *sodium carbonate R* and 0.05 g of *sodium hydrogen carbonate R* in *water R* and dilute to 1000 mL with the same solvent.

Flow rate 1.2 mL/min.

Detection Conductivity detector.

Injection 25 µL.

Retention time Sulfates = about 8 min.

Limit:

— *sulfates*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (4.0 per cent, expressed as sodium sulfate).

Iron (*2.4.9*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 400 ppm.

Dilute 2 mL of solution S to 40 mL with *water R*.

Loss on ignition

Maximum 25.0 per cent, determined on 0.200 g by heating in a platinum crucible at 100-105 °C for 1 h and then at 1000 ± 50 °C for 2 h.

ASSAY

To the residue obtained in the test for loss on ignition add 0.2 mL of *sulfuric acid R* and a quantity of *ethanol (96 per cent) R* sufficient to moisten the residue completely. Add 6 mL of *hydrofluoric acid R* and evaporate to dryness at 95-105 °C, taking care to avoid loss from sputtering. Wash the inside of the crucible with 6 mL of *hydrofluoric acid R* and evaporate to dryness again. Ignite at 900 ± 50 °C, allow to cool in a desiccator and weigh. The difference between the mass of the final residue and that of the mass obtained in the test for loss on ignition corresponds to the mass of SiO_2 in the test sample.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for dental type silica used as abrasive.

Specific surface area (*2.9.26, Method I*)

Determine the specific surface area in the P/P_0 range of 0.05 to 0.30.

Sample outgasing 60 min at 160 °C.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

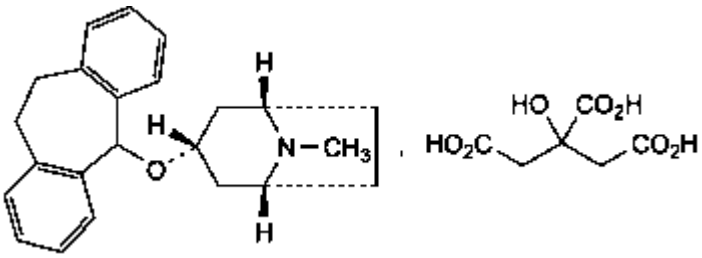
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Deptropine Citrate

General Notices

(Ph. Eur. monograph 1308)



$C_{29}H_{35}NO_8$ 525.6 *2169-75-7*

Action and use

Histamine H_1 receptor antagonist; anticholinergic.

Ph Eur

DEFINITION

Deptropine citrate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of (1*R*,3*r*,5*S*)-3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane dihydrogen citrate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, microcrystalline powder, very slightly soluble in water and in anhydrous ethanol, practically insoluble in methylene chloride.

It melts at about 170 °C, with decomposition.

IDENTIFICATION

First identification: A.

Second identification: B, C, D, E.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *deptropine citrate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (b).

C. To about 1 mg add 0.5 mL of *sulfuric acid R*. A stable red-orange colour develops.

D. Dissolve about 1 mg in 0.25 mL of *perchloric acid R* and warm gently until the solution becomes turbid. Add 5 mL of *glacial acetic acid R*; a pink colour with an intense green fluorescence appears.

E. To about 5 mg add 1 mL of *acetic anhydride R* and 5 mL of *pyridine R*. A purple colour develops.

TESTS

pH (*2.2.3*)

Suspend 0.25 g in *carbon dioxide-free water R*, dilute to 25 mL with the same solvent and filter. The pH of the solution is 3.7 to 4.5.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution (a) Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*.

Reference solution (b) Dissolve 20 mg of *deptropine citrate CRS* in *methanol R* and dilute to 2 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *methanol R*.

Reference solution (c) Dissolve 5 mg of *tropine CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (d) Dissolve 10 mg of *deptropine citrate CRS* and 10 mg of *tropine CRS* in *methanol R* and dilute to 25 mL with the same solvent.

Apply to the plate 40 µL of each solution. Develop over a path of 10 cm using a mixture of 8 volumes of *concentrated ammonia R* and 92 volumes of *butanol R*. Dry the plate at 100 °C to 105 °C until the ammonia has completely evaporated. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1 per cent). Spray with *dilute potassium iodobismuthate solution R* and then with a 10 g/L solution of *sodium nitrite R*. Expose the plate to iodine vapours. Examine in daylight and in ultraviolet light at 254 nm. In the chromatogram obtained with test solution (a): any spot corresponding to tropine is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.5 per cent); any spot, apart from the principal spot and any spot corresponding to tropine, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1 per cent). The test is not valid unless the chromatogram obtained with reference solution (d) shows two clearly separated spots.

Loss on drying (*2.2.32*)

Not more than 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

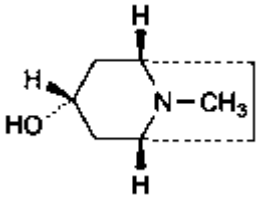
Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 52.56 mg of $C_{29}H_{35}NO_8$.

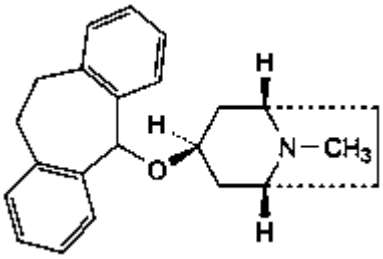
STORAGE

Store protected from light.

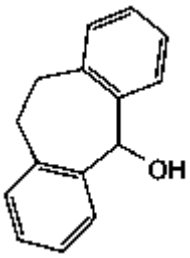
IMPURITIES



A. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (tropine),



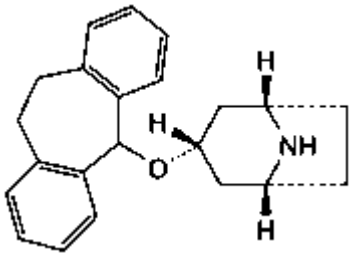
B. (1*R*,3*s*,5*S*)-3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane (pseudodeptropine),



C. 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol (dibenzocycloheptadienol),

www.webofpharma.com

https://thuvienthuocngocanh.com/



D. (1*R*,3*r*,5*S*)-3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-yloxy)-8-azabicyclo[3.2.1]octane (demethyldeptropine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

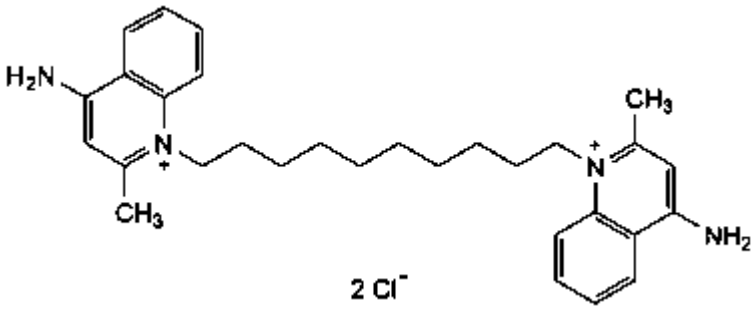
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Dequalinium Chloride

General Notices

(Ph. Eur. monograph 1413)



$C_{30}H_{40}Cl_2N_4$ 527.6 *522-51-0*

Action and use

Antiseptic.

Ph Eur

DEFINITION

1,1′-(Decane-1,10-diyl)bis(4-amino-2-methylquinolin-1-ium) dichloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or yellowish-white powder, hygroscopic.

Solubility

Slightly to very slightly soluble in water and slightly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve about 10 mg in *water R* and dilute to 100 mL with the same solvent. Dilute 10 mL of the solution to 100 mL with *water R*.

Spectral range 230-350 nm.

Absorption maxima At 240 nm and 326 nm.

Shoulder At 336 nm.

Absorbance ratios:

— A_{240}/A_{326} = 1.56 to 1.80;

— A_{326}/A_{336} = 1.12 to 1.30.

B. Infrared absorption spectrophotometry (2.2.24).

Spectral range 600-2000 cm^{-1}.

Comparison *dequalinium chloride for ID CRS*.

C. To 5 mL of solution S (see Tests) add 5 mL of *potassium ferricyanide solution R*. A yellow precipitate is formed.

D. To 10 mL of solution S add 1 mL of *dilute nitric acid R*. A white precipitate is formed. Filter and reserve the filtrate for identification test E.

E. To 10 mL of solution S (see Tests) add 1 mL of *dilute nitric acid R* and filter off the precipitate. The filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.2 g in 90 mL of *carbon dioxide-free water R*, heating if necessary, and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

www.webofpharma.com

https://thietbiuocngocanh.com/

To 5 mL of solution S add 0.1 mL of *bromothymol blue solution R1*. Not more than 0.2 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *dequalinium for system suitability CRS* (containing impurities A, B and C) in the mobile phase and dilute to 5 mL with the mobile phase.

Reference solution (b) Dissolve 10.0 mg of *dequalinium chloride for ID CRS* (with an assigned content) in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 2 g of *sodium hexanesulfonate R* in 300 mL of *water for chromatography R*; adjust to pH 4.0 with *acetic acid R* and add 700 mL of *methanol R1*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 10 µL.

Run time 5 times the retention time of dequalinium.

Identification of impurities Use the chromatogram supplied with *dequalinium for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to dequalinium (retention time = about 4 min): impurity A = about 0.5; impurity B = about 1.3; impurity C = about 4.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to dequalinium.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.5; impurity C = 1.5;

www.webofpharma.com

https://thuocngocanh.com/

— for each impurity, use the concentration of dequalinium chloride in reference solution (b), taking into account the assigned content of *dequalinium chloride for ID CRS*.

Limits:

— *impurity C*: maximum 5.0 per cent;

— *impurity B*: maximum 2.0 per cent;

— *impurity A*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 7.0 per cent;

— *reporting threshold*: 0.05 per cent.

Readily carbonisable substances

Dissolve 20 mg in 2 mL of *sulfuric acid R*. After 5 min the solution is not more intensely coloured than reference solution BY_4 (*2.2.2, Method I*).

Water (*2.5.12*)

Maximum 10.0 per cent, determined on 0.08 g. Use as the solvent a mixture of equal volumes of *methanol R* and *formamide R*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.200 g in 5 mL of *formic acid R* and add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 26.38 mg of $C_{30}H_{40}Cl_2N_4$.

STORAGE

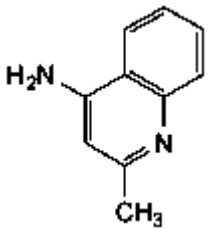
In an airtight container.

IMPURITIES

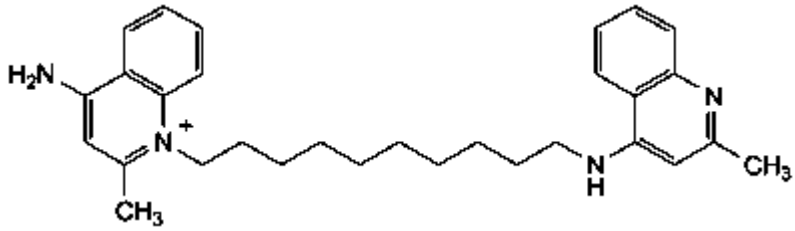
Specified impurities *A, B, C.*

www.webofpharma.com

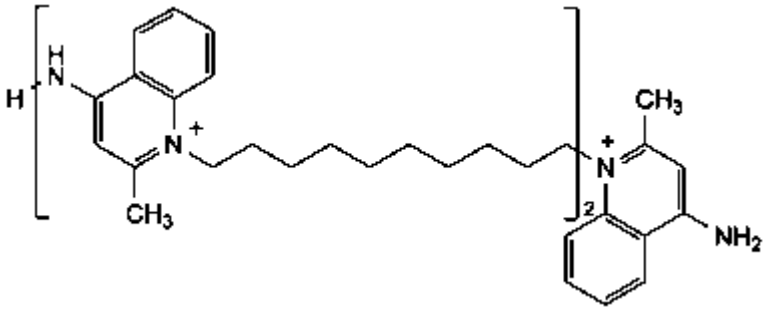
https://thuocngocanh.com/



A. 2-methylquinolin-4-amine,



B. 4-amino-2-methyl-1-[10-[(2-methylquinolin-4-yl)amino]decyl]quinolin-1-ium,



C. 4-amino-1-[10-[[1-[10-(4-amino-2-methylquinolin-1-ium-1-yl)decyl]-2-methylquinolin-1-ium-4-yl]amino]decyl]-2-methylquinolin-1-ium.

Ph Eur

© Crown Copyright 2022

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desferrioxamine Injection

General Notices

Action and use

Chelating agent (iron).

DEFINITION

Desferrioxamine Injection is a sterile solution of Desferrioxamine Mesilate in Water for Injections. It is prepared by dissolving Desferrioxamine Mesilate for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Desferrioxamine Injection deteriorates on storage and should be used immediately after preparation. Cloudy solutions should be discarded.

DESFERRIOXAMINE MESILATE FOR INJECTION

DEFINITION

Desferrioxamine Mesilate for Injection is a sterile material consisting of Desferrioxamine Mesilate with or without excipients. It is supplied in a sealed container.

PRODUCTION

Risk assessment should be used to evaluate the potential for genotoxic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of desferrioxamine mesilate, $C_{25}H_{48}N_6O_8,CH_4SO_3$

94.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dissolve 40 mg of the contents of the sealed container in 2 mL of *absolute ethanol* by heating on a water bath at 60°, cool in ice until the substance begins to crystallise and evaporate to dryness at room temperature under a gentle current of *nitrogen*. The *infrared*

www.webofpharma.com

https://thuocngocanh.com/

absorption spectrum of the residue, Appendix II A, is concordant with the *reference spectrum* of desferrioxamine mesilate *(RS 086)*.

B. In the test for Related substances the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (3).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

(1) Dissolve a quantity of the contents of the sealed containers containing 75 mg of Desferrioxamine Mesilate in sufficient of the mobile phase to produce 50 mL.

(2) Dilute 1 volume of solution (1) to 25 volumes with the mobile phase.

(3) 0.15% w/v of *desferrioxamine mesilate BPCRS* in the mobile phase.

(4) Dilute 1 volume of solution (2) to 50 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 20 µL of each solution.

(g) For solutions (1) and (2) allow the chromatography to proceed for three times the retention time of the principal peak.

MOBILE PHASE

55 volumes of *tetrahydrofuran* and 950 volumes of a solution containing 0.039% w/v of *disodium edetate* and 0.139% w/v of *ammonium phosphate* adjusted to pH 2.8 with *orthophosphoric acid* in *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak with relative retention time of about 0.8 and the principal peak is at least 1.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (4%);

the sum of the areas of any such peaks is not greater than 1.75 times the area of the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.08%).

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Use.

Dissolve a quantity of the mixed contents of the 10 containers containing 0.3 g of Desferrioxamine Mesilate in 15 mL of *water* and add 2 mL of 0.05M *sulfuric acid*. Titrate slowly with 0.1M *ammonium iron(III) sulfate VS* determining the end point potentiometrically and using a platinum electrode and a calomel reference electrode. Each mL of 0.1M *ammonium iron(III) sulfate VS* is equivalent to 65.68 mg of $C_{25}H_{48}N_6O_8,CH_4SO_3$. Calculate the content of $C_{25}H_{48}N_6O_8,CH_4SO_3$ in a container of average content weight.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

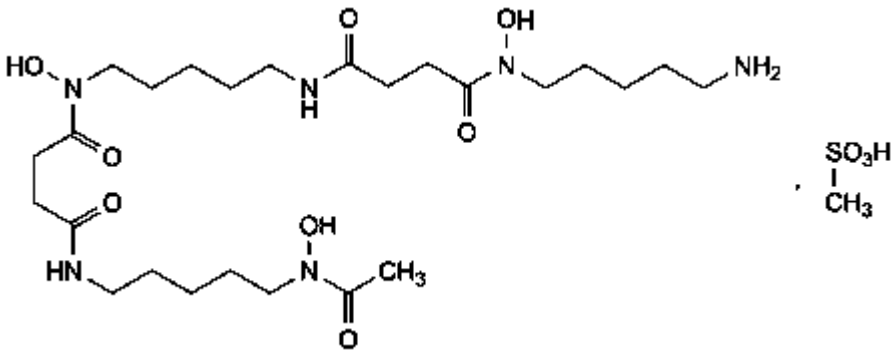
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desferrioxamine Mesilate

General Notices

(Deferoxamine Mesilate, Ph. Eur. monograph 0896)



$C_{26}H_{52}N_6O_{11}S$ 657 *138-14-7*

Action and use

Chelating agent (iron).

Preparation

Desferrioxamine Injection

Ph Eur

DEFINITION

N^1-[5-(4-[(5-Aminopentyl)(hydroxy)amino]-4-oxobutanamido)pentyl]-N^1-hydroxy-N^4-[5-(*N*-hydroxyacetamido)pentyl]butanediamide methanesulfonate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in deferoxamine mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

www.webofpharma.com

https://thuocngocanh.com/

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, slightly soluble in methanol, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *deferoxamine mesilate CRS*.

B. Dissolve 0.1 g in 5 mL of *dilute hydrochloric acid R*. Add 1 mL of *barium chloride solution R2*. The solution is clear. In a porcelain crucible, mix 0.1 g with 1 g of *anhydrous sodium carbonate R*, heat and ignite over a naked flame. Allow to cool. Dissolve the residue in 10 mL of *water R*, heating if necessary, and filter. The filtrate gives reaction (a) of sulfates (2.3.1).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

pH (2.2.3)

4.0 to 6.0.

Dilute 1 mL of freshly prepared solution S to 10 mL with *carbon dioxide-free water R* prepared from *distilled water R*.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light*.

A. Deferoxamine mesilate produced by fermentation.

Solvent mixture *acetonitrile R*, *water R* (6:94 *V/V*).

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 5 mg of *deferoxamine for system suitability CRS* (containing impurity A) in mobile phase A and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.075 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 32 °C.

Mobile phase:

— *mobile phase A*: 1.32 g/L solution of *ammonium phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: mixture of equal volumes of *acetonitrile for chromatography R* and mobile phase A;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	88	12
4 - 20	88 → 80	12 → 20
20 - 35	80 → 57.5	20 → 42.5

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to deferoxamine (retention time = about 18 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and deferoxamine.

Calculation of percentage contents:

— for each impurity, use the concentration of deferoxamine mesilate in reference solution (a).

Limits:

— *impurity A*: maximum 2.0 per cent;

— *any other impurity*: for each impurity, maximum 0.8 per cent;

www.webofpharma.com

https://thietbiuocngocanh.com/

— *total*: maximum 5.0 per cent;

— *reporting threshold*: 0.05 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

B. Deferoxamine mesilate produced by a synthetic process.

Solvent mixture Mobile phase B, mobile phase A (20:80 *V/V*).

Test solution Dissolve 0.125 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 12.5 mg of *deferoxamine for peak identification CRS* (containing impurities F, G, H, I and J) in the solvent mixture and dilute to 1 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.605 g of *sodium edetate R* in 900 mL of *water for chromatography R*, add 1.0 mL of *phosphoric acid R* and adjust to pH 6.0 with *concentrated ammonia R*; dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: dissolve 0.780 g of *sodium edetate R* in 750 mL of *water for chromatography R* and add 1.0 mL of *phosphoric acid R*; add 250 mL of *acetonitrile for chromatography R*, mix thoroughly and adjust the apparent pH to 6.0 with *concentrated ammonia R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0	80	20
0 - 21.6	80 → 20	20 → 80
21.6 - 31.6	20	80

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *deferoxamine for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities F, G, H, I and J.

Relative retention With reference to deferoxamine (retention time = about 12.9 min): impurity I = about 0.5; impurity F = about 0.96; impurity G = about 0.98; impurity H = about 1.2; impurities J and K = about 1.37.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to deferoxamine.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity I by 1.4;

— for each impurity, use the concentration of deferoxamine mesilate in reference solution (a).

Limits:

— *impurities F, H*: for each impurity, maximum 0.5 per cent;

— *impurities G, I*: for each impurity, maximum 0.3 per cent;

— *sum of impurities J and K*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.20 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.03 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Chlorides (*2.4.4*)

Maximum 330 ppm.

Dilute 2 mL of solution S to 20 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 400 ppm.

Dilute 5 mL of solution S to 20 mL with *distilled water R*.

Water (*2.5.12*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 2.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.025 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. Since deferoxamine mesilate has an inhibitory effect on the bacterial endotoxins test, a suitable procedure is put in place to remove this inhibitory effect. The monocyte-activation test (*2.6.30*) has been found suitable to overcome this issue.

ASSAY

Dissolve 0.500 g in 50 mL of *water R*. Add 4 mL of *dilute sulfuric acid R1*. Titrate with *0.1 M ferric ammonium sulfate*. To accelerate the titration, add 4.5 mL quickly, stop for 1.5 min and continue to titrate uniformly at a rate of about 0.2 mL/min. Determine the end-point potentiometrically (*2.2.20*) using a platinum indicator electrode and a suitable reference electrode.

1 mL of *0.1 M ferric ammonium sulfate* is equivalent to 65.68 mg of $C_{26}H_{52}N_6O_{11}S$.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

The label states the origin of the substance:

— produced by fermentation;

— produced by a synthetic process.

IMPURITIES

Test A for related substances: A, B, C, J.

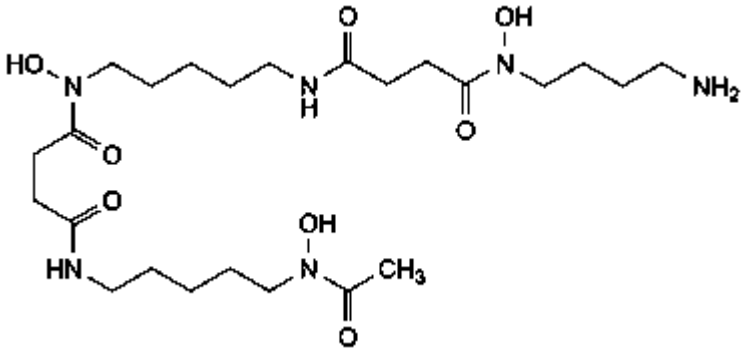
Test B for related substances: E, F, G, H, I, J, K.

Specified impurities *A, F, G, H, I, J, K.*

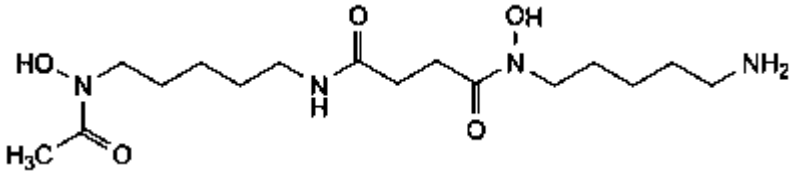
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, E.*

www.webofpharma.com

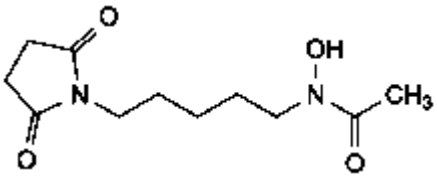
https://thuocngocanh.com/



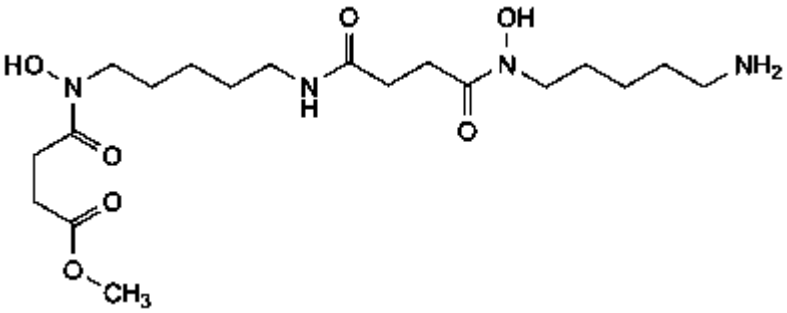
A. N^1-[5-(4-[(4-aminobutyl)(hydroxy)amino]-4-oxobutanamido)pentyl]-N^1-hydroxy-N^4-[5-(*N*-hydroxyacetamido)pentyl]butanediamide,



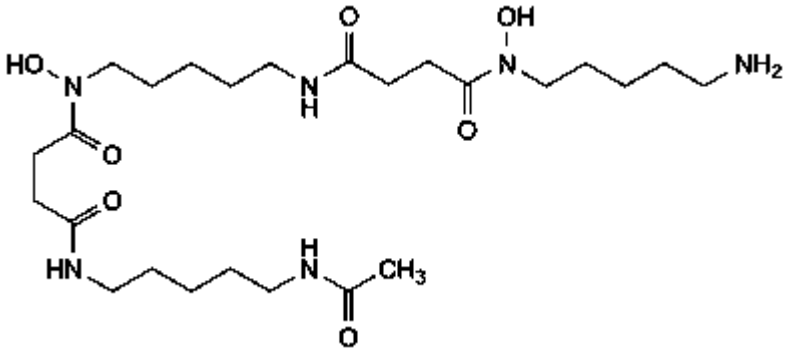
B. N^1-(5-aminopentyl)-N^1-hydroxy-N^4-[5-(*N*-hydroxyacetamido)pentyl]butanediamide,



C. *N*-[5-(2,5-dioxopyrrolidin-1-yl)pentyl]-*N*-hydroxyacetamide,



E. methyl 4-[[5-[[4-[(5-aminopentyl)(hydroxy)amino]-4-oxobutanamido]pentyl](hydroxy)amino]-4-oxobutanoate,

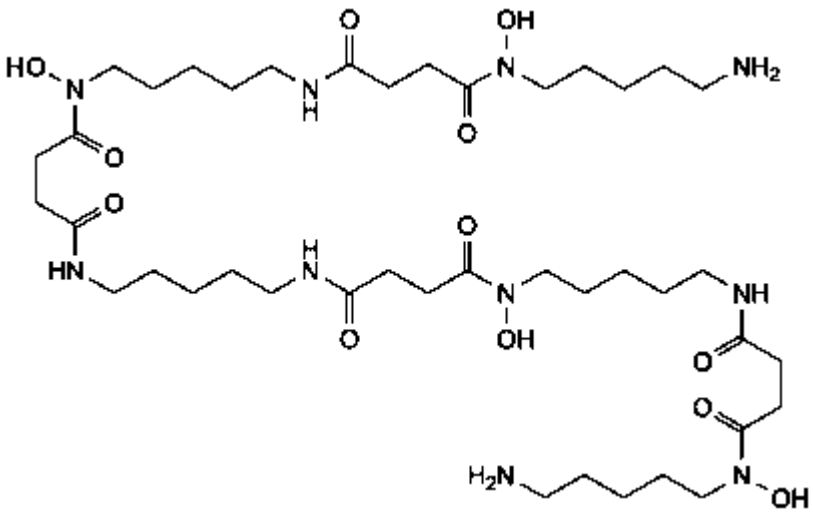


www.webofpharma.com

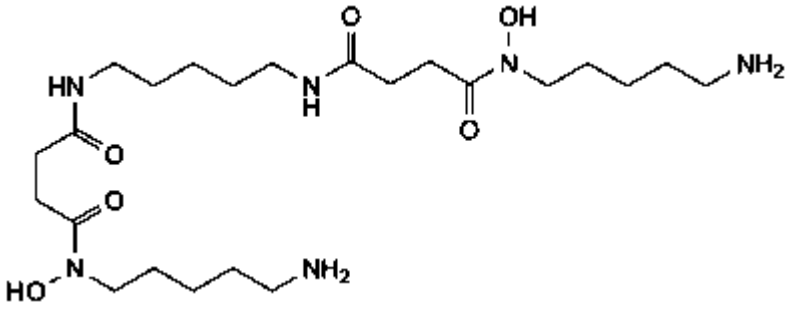
https://thuocngocanh.com/

F. N^1-(5-acetamidopentyl)-N^4-[5-[4-[(5-aminopentyl)(hydroxyl)amino]-4-oxobutanamido]pentyl]-N^4-hydroxybutanediamide,

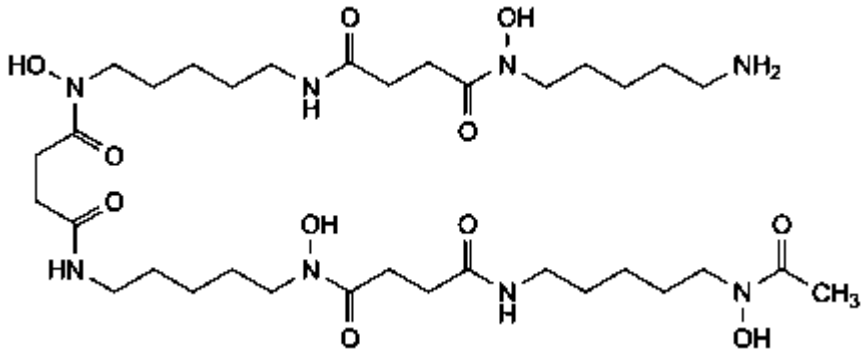
G. unknown structure,



H. N^1,N^{37}-bis(5-aminopentyl)-N^1,N^{37},11,27-tetrahydroxy-4,12,15,23,26,34-hexaoxo-5,11,16,22,27,33-hexaazaheptatriacontane-1,37-diamide,



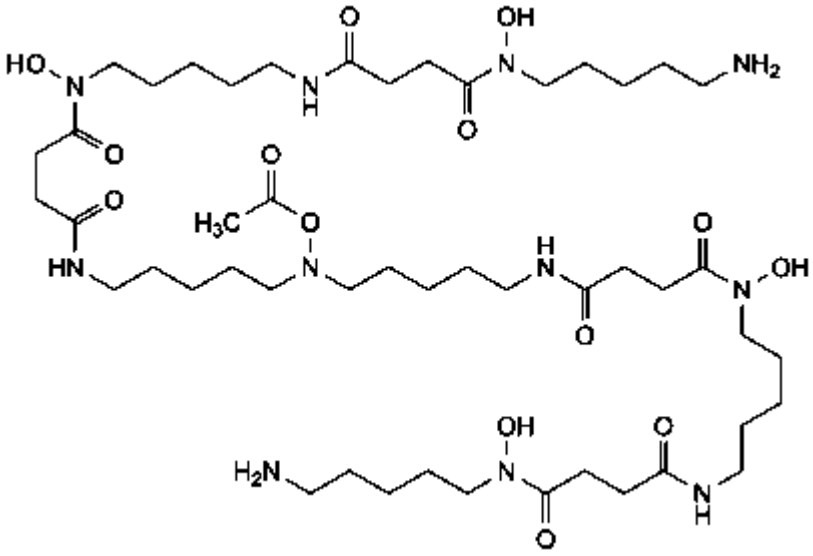
I. N^1-(5-aminopentyl)-N^4-[5-(4-[(5-aminopentyl)(hydroxy)amino]-4-oxobutanamido)pentyl]- N^1-hydroxybutanediamide,



J. N^1-(5-aminopentyl)-N^1,11,22-trihydroxy-N^{26}-[5-(*N*-hydroxyacetamido)pentyl]-4,12,15,23-tetraoxo-5,11,16,22-tetraazahexacosane-1,26-diamide,

www.webofpharma.com

https://thuocngocanh.com/



K. 22-(acetyloxy)-N^1,N^{43}-bis(5-aminopentyl)-N^1,N^{43},11,33-tetrahydroxy-4,12,15,29,32,40-hexaoxo-5,11,16,22,28,33,39-heptaazatritetracontane-1,43-diamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

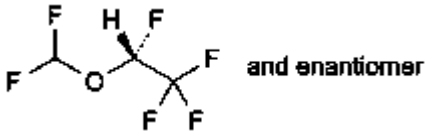
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desflurane

General Notices

(Ph. Eur. monograph 1666)



$C_3H_2F_6O$ 168.0 *57041-67-5*

Ph Eur

DEFINITION

(2*RS*)-2-(Difluoromethoxy)-1,1,1,2-tetrafluoroethane.

CHARACTERS

Appearance

Clear, colourless, mobile, heavy liquid.

Solubility

Practically insoluble in water, miscible with anhydrous ethanol.

Relative density

1.47, determined at 15 °C.

bp

About 22 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Preparation Examine the substance in the gaseous state.

Comparison *Ph. Eur. reference spectrum of desflurane*.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

TESTS

The substance to be examined must be cooled to a temperature below 10 °C and the tests must be carried out at a temperature below 20 °C.

Acidity or alkalinity

To 20 mL add 20 mL of *carbon dioxide-free water R*, shake for 3 min and allow to stand. Collect the upper layer and add 0.2 mL of *bromocresol purple solution R*. Not more than 0.1 mL of *0.01 M sodium hydroxide* or 0.6 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Related substances

Gas chromatography (*2.2.28*).

Test solution The substance to be examined.

Reference solution (a) Introduce 25 mL of the substance to be examined into a 50 mL flask fitted with a septum, and add 0.50 mL of *desflurane impurity A CRS* and 1.0 mL of *isoflurane CRS* (impurity B). Add 50 µL of *acetone R* (impurity H), 10 µL of *chloroform R* (impurity F) and 50 µL of *methylene chloride R* (impurity E) to the solution, using an airtight syringe, and dilute to 50.0 mL with the substance to be examined. Dilute 5.0 mL of this solution to 50.0 mL with the substance to be examined. Store at a temperature below 10 °C.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the substance to be examined. Store at a temperature below 10 °C.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 25.0 mL with the substance to be examined. Store at a temperature below 10 °C.

Column:

— *material*: fused silica;

— *size*: *l* = 105 m, Ø = 0.32 mm;

— *stationary phase*: *trifluoropropylmethylpolysiloxane R* (film thickness 1.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.0 mL/min.

Split ratio 1:25.

Temperature:

— *column*: 30 °C;

— *injection port*: 150 °C;

www.webofpharma.com

https://thuocngocanh.com/

— *detector*: 200 °C.

Detection Flame ionisation.

Injection 2.0 µL.

Run time 35 min.

Relative retention With reference to desflurane (retention time = about 11.5 min): impurity C = about 1.06; impurity D = about 1.09; impurity A = about 1.14; impurity G = about 1.39; impurity E = about 1.5; impurity B = about 1.7; impurity F = about 2.2; impurity H = about 2.6.

System suitability Reference solution (a):

— *number of theoretical plates*: minimum 20 000, calculated for the peak due to impurity A;

— *symmetry factor*: maximum 2.0 for the peak due to impurity B.

Limits:

— *impurity B*: not more than the difference between the area of the corresponding peak in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.2 per cent *V/V*);

— *impurity A*: not more than the difference between the area of the corresponding peak in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.1 per cent *V/V*);

— *impurities C, D, G*: for each impurity, not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.01 per cent *V/V*);

— *impurities E, H*: for each impurity, not more than the difference between the area of the corresponding peak in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.01 per cent *V/V*);

— *impurity F*: not more than the difference between the area of the corresponding peak in the chromatogram obtained with reference solution (a) and the area of the corresponding peak in the chromatogram obtained with the test solution (0.002 per cent *V/V*);

— *unspecified impurities*: for each impurity, not more than 0.5 times the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.005 per cent *V/V*);

— *sum of impurities other than A, B, C, D, E, F, G and H*: not more than the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (b) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.01 per cent *V/V*);

— *disregard limit*: the difference between the area of the peak due to impurity A in the chromatogram obtained with reference solution (c) and the area of the peak due to impurity A in the chromatogram obtained with the test solution (0.002 per cent *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Fluorides

Maximum 10 ppm.

Potentiometry (*2.2.36, Method I*).

Test solution To 10.0 mL in a separating funnel, add 10 mL of a mixture of 30.0 mL of *dilute ammonia R2* and 70.0 mL of *distilled water R*. Shake for 1 min and collect the upper layer. Repeat this extraction procedure twice, collecting the upper layer each time. Adjust the combined upper layers to pH 5.2 with *dilute hydrochloric acid R*. Add 5.0 mL of *fluoride standard solution (1 ppm F) R* and dilute to 50.0 mL with *distilled water R*. To 20.0 mL of this solution add 20.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50.0 mL with *distilled water R*.

Reference solutions To each of 1.0 mL, 2.0 mL, 3.0 mL, 4.0 mL and 5.0 mL of *fluoride standard solution (10 ppm F) R* add 20.0 mL of *total-ionic-strength-adjustment buffer R* and dilute to 50.0 mL with *distilled water R*.

Indicator electrode Fluoride selective.

Reference electrode Silver-silver chloride.

Carry out the measurements on 20 mL of each solution. Calculate the concentration of fluorides using the calibration curve, taking into account the addition of fluoride to the test solution.

Non-volatile matter

Maximum 100 mg/L.

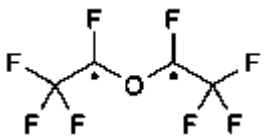
Evaporate 20.0 mL to dryness with the aid of a stream of *nitrogen R*. The residue weighs not more than 2.0 mg.

STORAGE

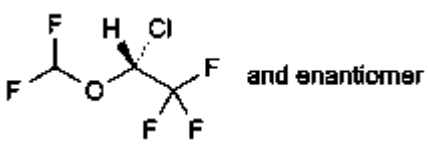
In a glass bottle fitted with a polyethylene-lined cap. Before opening the bottle, cool the contents to below 10 °C.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G, H.*

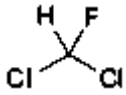


A. 1,1′-oxybis[(1Ξ)-1,2,2,2-tetrafluoroethane],

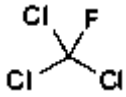


https://thuocngocanh.com/

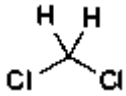
B. (2*RS*)-2-chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane (isofluorane),



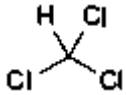
C. dichlorofluoromethane,



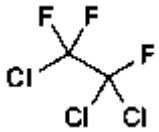
D. trichlorofluoromethane,



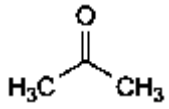
E. dichloromethane (methylene chloride),



F. trichloromethane (chloroform),



G. 1,1,2-trichloro-1,2,2-trifluoroethane,



H. propan-2-one (acetone).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

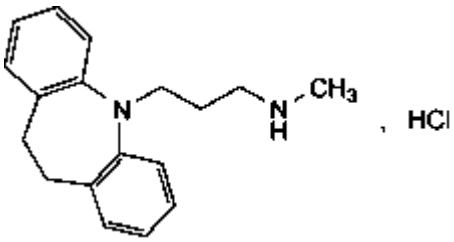
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desipramine Hydrochloride

General Notices

(Ph. Eur. monograph 0481)



$C_{18}H_{23}ClN_2$ 302.8 *58-28-6*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparation

Desipramine Tablets

Ph Eur

DEFINITION

3-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*-methylpropan-1-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water and in anhydrous ethanol, practically insoluble in heptane.

mp

www.webofpharma.com

https://thuocngocanh.com/

About 214 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *desipramine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.25 g in *carbon dioxide-free water R*, warming to not more than 30 °C if necessary, and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S, examined immediately after preparation, is not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.3 mL of *0.01 M sodium hydroxide*. The solution is yellow. Not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 5.2 g of *dipotassium hydrogen phosphate R* in 1000 mL of *water for chromatography R*, add 1 mL of *triethylamine R* and adjust to pH 6.4 with *phosphoric acid R*.

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of *imipramine hydrochloride R* (impurity A) in mobile phase A and dilute to 100 mL with mobile phase A. Mix 1 mL of the solution and 9 mL of the test solution, and dilute to 100 ml with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 60 °C.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: *methanol R*, *acetonitrile R*, buffer solution (11:14:75 *V/V/V*);

— *mobile phase B*: *methanol R*, *acetonitrile R*, buffer solution (28:34:38 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 37	85 → 0	15 → 100
37 - 52	0	100

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 40 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to desipramine (retention time = about 19 min): impurity A = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 25 between the peaks due to desipramine and impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of desipramine hydrochloride in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thietbiuocngocanh.com/

Dissolve 0.250 g in a mixture of 5 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

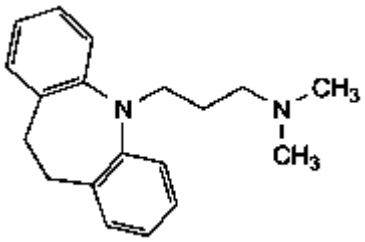
1 mL of *0.1 M sodium hydroxide* is equivalent to 30.28 mg of $C_{18}H_{23}ClN_2$.

STORAGE

Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



A. 3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine (imipramine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

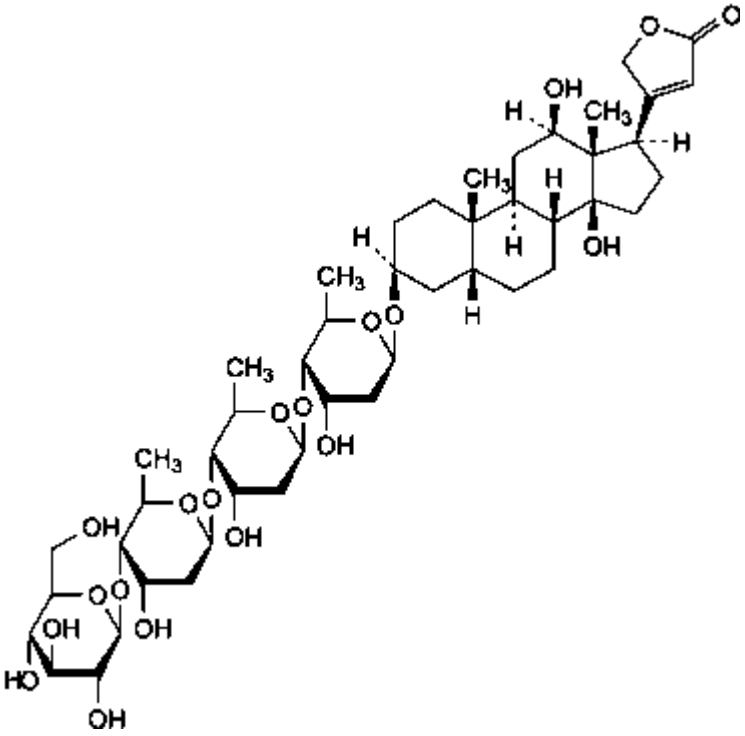
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Deslanoside

General Notices

(Ph. Eur. monograph 0482)



$C_{47}H_{74}O_{19}$ 943 *17598-65-1*

Action and use

Na/K-ATPase inhibitor; cardiac glycoside.

Ph Eur

DEFINITION

Deslanoside contains not less than 95.0 per cent and not more than the equivalent of 105.0 per cent of 3β-[(*O*-β-D-glucopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β,14β-card-20(22)-enolide, calculated with reference to the dried substance.

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

A white or almost white, crystalline or finely crystalline powder, hygroscopic, practically insoluble in water, very slightly soluble in ethanol (96 per cent). In an atmosphere of low relative humidity, it loses water.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with deslanoside CRS. When comparing the spectra, special attention is given to the absence of a distinct absorption maximum at about 1260 cm^{-1} and to the intensity of the absorption maximum at about 1740 cm^{-1}. Examine the substances in discs prepared by dissolving 1 mg of the substance to be examined or 1 mg of the reference substance in 0.3 mL of methanol R and triturating with about 0.4 g of dry, finely powdered potassium bromide R until the mixture is uniform and completely dry.

B. Examine the chromatograms obtained in the test for related substances. The principal zone in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal zone in the chromatogram obtained with reference solution (a).

C. Suspend about 0.5 mg in 0.2 mL of alcohol (60 per cent V/V) R. Add 0.1 mL of dinitrobenzoic acid solution R and 0.1 mL of dilute sodium hydroxide solution R. A violet colour develops.

D. Dissolve about 5 mg in 5 mL of glacial acetic acid R and add 0.05 mL of ferric chloride solution R1. Cautiously add 2 mL of sulfuric acid R, avoiding mixing the two liquids. Allow to stand; a brown but not reddish ring develops at the interface and a greenish-yellow, then bluish-green colour diffuses from it to the upper layer.

TESTS

Solution S

Dissolve 0.20 g in a mixture of equal volumes of chloroform R and methanol R and dilute to 10 mL with the same mixture of solvents.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Specific optical rotation (2.2.7)

Dissolve 0.200 g in anhydrous pyridine R and dilute to 10.0 mL with the same solvent. The specific optical rotation is + 6.5 to + 8.5, calculated with reference to the dried substance.

Related substances

Examine by thin-layer chromatography (2.2.27), using silica gel G R as the coating substance.

Test solution (a) Use solution S.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with a mixture of equal volumes of chloroform R and methanol R.

www.webofpharma.com

https://thietbiuocngocanh.com/

Reference solution (a) Dissolve 20 mg of *deslanoside CRS* in a mixture of equal volumes of *chloroform R* and *methanol R* and dilute to 10 mL with the same mixture of solvents.

Reference solution (b) Dilute 2.5 mL of reference solution (a) to 10 mL with a mixture of equal volumes of *chloroform R* and *methanol R*.

Reference solution (c) Dilute 1 mL of reference solution (a) to 10 mL with a mixture of equal volumes of *chloroform R* and *methanol R*.

Apply separately to the plate as 10 mm bands 5 µL of each solution. Develop immediately over a path of 15 cm using a mixture of 3 volumes of *water R*, 36 volumes of *methanol R* and 130 volumes of *methylene chloride R*. Dry the plate in a current of warm air, spray with a mixture of 5 volumes of *sulfuric acid R* and 95 volumes of *alcohol R* and heat at 140 °C for 15 min. Examine in daylight. In the chromatogram obtained with test solution (a), any zone, apart from the principal zone, is not more intense than the zone in the chromatogram obtained with reference solution (b) (2.5 per cent) and at most two such zones are more intense than the zone in the chromatogram obtained with reference solution (c) (1.0 per cent).

Loss on drying (*2.2.32*)

Not more than 5.0 per cent, determined on 0.500 g by drying *in vacuo* at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

Dissolve 50.0 mg in *alcohol R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *alcohol R*. Prepare a reference solution in the same manner, using 50.0 mg of *deslanoside CRS* (undried). To 5.0 mL of each solution add 3.0 mL of *alkaline sodium picrate solution R* and allow to stand protected from bright light in a water-bath at 20 ± 1 °C for 40 min. Measure the absorbance (*2.2.25*) of each solution at the maximum at 484 nm, using as the compensation liquid a mixture of 3.0 mL of *alkaline sodium picrate solution R* and 5.0 mL of *alcohol R* prepared at the same time.

Calculate the content of $C_{47}H_{74}O_{19}$ from the absorbances measured and the concentrations of the solutions.

STORAGE

Store in an airtight, glass container, protected from light, at a temperature below 10 °C.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thietbiuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

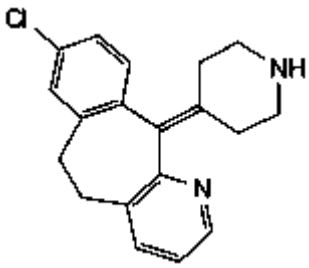
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desloratadine

General Notices

(Ph. Eur. monograph 2570)



$C_{19}H_{19}ClN_2$ 310.8 *100643-71-8*

Action and use

Histamine H1, receptor antagonist; antihistamine.

Ph Eur

DEFINITION

8-Chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble or practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble or very slightly soluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison desloratadine CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methyl isobutyl ketone R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 20.0 mg of desloratadine CRS in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 4 mg of desloratadine for system suitability CRS (containing impurities A and B) in the mobile phase and dilute to 5.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (4 µm);

— *temperature*: 35 °C.

Mobile phase Dissolve 0.865 g of sodium dodecyl sulfate R in water R, add 0.5 mL of trifluoroacetic acid R and dilute to 1000 mL with water R; mix 57 volumes of this solution and 43 volumes of acetonitrile R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 100 µL of the test solution and reference solutions (b) and (c).

Run time 2.5 times the retention time of desloratadine.

Identification of impurities Use the chromatogram supplied with desloratadine for system suitability CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to desloratadine (retention time = about 21 min): impurity A = about 0.8; impurity B = about 0.9.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to impurity B and desloratadine.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.6; impurity B = 1.6;

— for each impurity, use the concentration of desloratadine in reference solution (b).

Limits:

— *impurity B*: maximum 0.3 per cent;

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 0.5 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

— *symmetry factor*: 0.5 to 1.5 for the peak due to desloratadine.

Calculate the percentage content of $C_{19}H_{19}ClN_2$ taking into account the assigned content of *desloratadine CRS*.

IMPURITIES

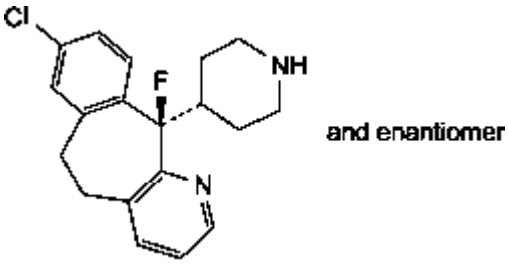
Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

www.webofpharma.com

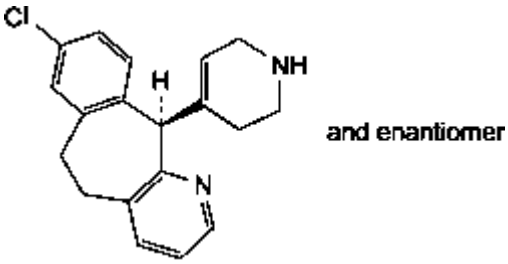
https://thuocngocanh.com/

Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



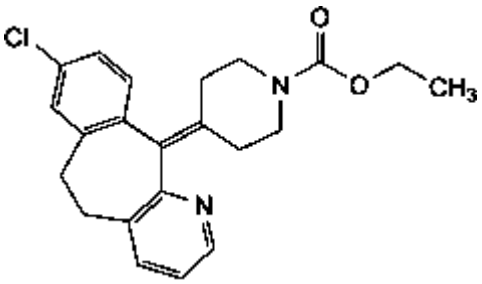
and enantiomer

A. (11*RS*)-8-chloro-11-fluoro-11-(piperidin-4-yl)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine,



and enantiomer

B. (11*RS*)-8-chloro-11-(1,2,3,6-tetrahydropyridin-4-yl)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine,



C. ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (loratadine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

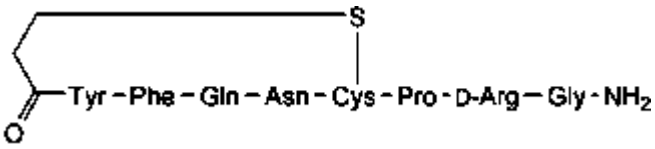
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desmopressin

General Notices

(Ph. Eur. monograph 0712)



$C_{46}H_{64}N_{14}O_{12}S_2$ 1069 *16679-58-6*

Action and use

Vasopressin analogue; treatment of diabetes insipidus; nocturnal enuresis; haemophilia; von Willebrand's disease.

Preparations

Desmopressin Injection

Desmopressin Intranasal Solution

Desmopressin Nasal Spray

Desmopressin Oral Lyophilisate

Desmopressin Tablets

Ph Eur

DEFINITION

(3-Sulfanylpropanoyl)-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-D-arginylglycinamide cyclic (1→6)-disulfide.

Synthetic cyclic nonapeptide, available as an acetate.

Content

95.0 per cent to 105.0 per cent (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance

White or almost white, fluffy powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Soluble in water, in ethanol (96 per cent) and in glacial acetic acid.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The retention time and size of the principal peak in the chromatogram obtained with the test solution are approximately the same as those of the principal peak in the chromatogram obtained with the reference solution.

B. Amino acid analysis (*2.2.56*). For hydrolysis use Method 1 and for analysis use Method 1.
Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids, taking 1/6 of the sum of the number of moles of aspartic acid, glutamic acid, proline, glycine, arginine and phenylalanine as equal to 1. The values fall within the following limits: aspartic acid: 0.90 to 1.10; glutamic acid: 0.90 to 1.10; proline: 0.90 to 1.10; glycine: 0.90 to 1.10; arginine: 0.90 to 1.10; phenylalanine: 0.90 to 1.10; tyrosine: 0.70 to 1.05; half-cystine: 0.30 to 1.05. Lysine, isoleucine and leucine are absent; not more than traces of other amino acids are present.

TESTS

Specific optical rotation (*2.2.7*)

-72 to -82 (anhydrous and acetic acid-free substance).

Dissolve 10.0 mg in a 1 per cent *V/V* solution of *glacial acetic acid R* and dilute to 5.0 mL with the same acid.

Related substances

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 1.0 mg of the substance to be examined in 2.0 mL of *water R*.

Resolution solution Dissolve the contents of a vial of *oxytocin/desmopressin validation mixture CRS* in 500 µL of *water R*.

Column:

— *size*: *l* = 0.12 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *0.067 M phosphate buffer solution pH 7.0 R*; filter and degas;

— *mobile phase B*: *acetonitrile for chromatography R*, mobile phase A (50:50 *V/V*); filter and degas.

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	76	24
4 - 18	76 → 58	24 → 42
18 - 35	58 → 48	42 → 52
35 - 40	48 → 76	52 → 24
40 - 50	76	24

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 50 µL.

Retention time Desmopressin = about 16 min; oxytocin = about 17 min.

System suitability Resolution solution:

— *resolution*: minimum 1.5 between the peaks due to desmopressin and oxytoxin.

Limits:

— *unspecified impurities*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 1.5 per cent;

— *disregard limit*: 0.05 per cent.

Acetic acid (*2.5.34*)

3.0 per cent to 8.0 per cent.

Test solution Dissolve 20.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of mobile phases.

Water (*2.5.32*)

Maximum 6.0 per cent, determined on 20.0 mg.

Bacterial endotoxins (*2.6.14*)

Less than 500 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Reference solution Dissolve the contents of a vial of *desmopressin CRS* in *water R* to obtain a concentration of 0.5 mg/mL.

Mobile phase Mobile phase B, mobile phase A (40:60 *V/V*).

Flow rate 2.0 mL/min.

Retention time Desmopressin = about 5 min.

Calculate the content of desmopressin ($C_{46}H_{64}N_{14}O_{12}S_2$) from the declared content of $C_{46}H_{64}N_{14}O_{12}S_2$ in *desmopressin CRS*.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

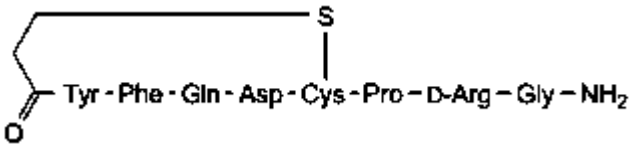
The label states:

— the mass of peptide per container;

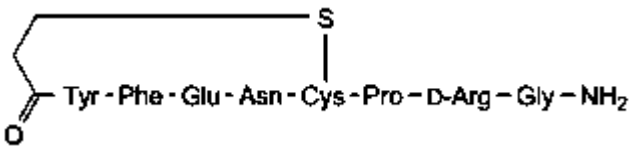
— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G.*



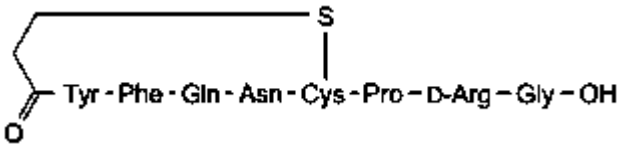
A. [5-L-aspartic acid]desmopressin,



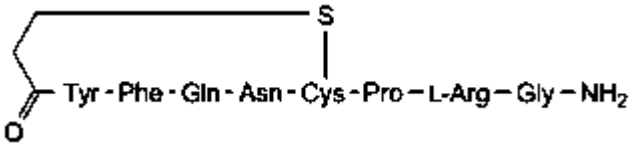
B. [4-L-glutamic acid]desmopressin,

www.webofpharma.com

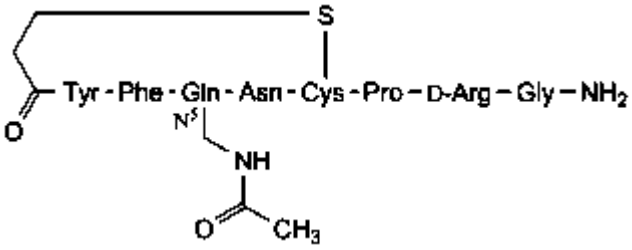
https://thuocngocanh.com/



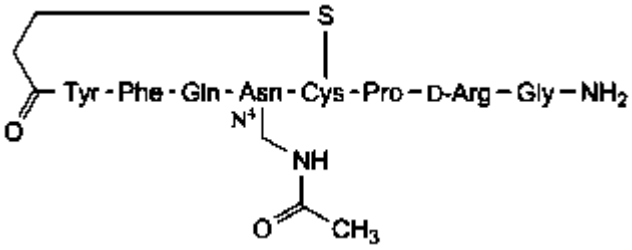
C. [9-glycine]desmopressin,



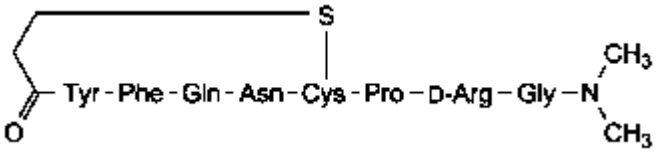
D. [8-L-arginine]desmopressin,



E. $N^{5.4}$-[(acetylamino)methyl]desmopressin,



F. $N^{4.5}$-[(acetylamino)methyl]desmopressin,



G. $N^{1.9}$,$N^{1.9}$-dimethyldesmopressin.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desmopressin Injection

General Notices

Action and use

Vasopressin analogue; treatment of diabetes insipidus; nocturnal enuresis; haemophillia; von Willebrand's disease.

DEFINITION

Desmopressin Injection is a sterile solution of Desmopressin in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of desmopressin, $C_{46}H_{64}N_{14}O_{12}S_2$

90.0 to 110.0% of the stated amount of the peptide.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*.

(1) Dilute the injection, if necessary, with *water* to produce a solution containing 0.0004% w/v of the peptide.

(2) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 2 mL of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12 cm x 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A *0.067M mixed phosphate buffer solution pH 7.0*.

Mobile phase B A mixture of *acetonitrile for chromatography* and mobile phase A in equal volumes.

Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0-4	76	24	isocratic
4-18	76→58	24→42	linear gradient
18-35	58→48	42→52	linear gradient
35-40	48→76	52→24	linear gradient
40-50	76	24	re-equilibration

The retention time of [4- L -glutamic acid]desmopressin is about 14 minutes and the retention time of desmopressin is about 15 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 3.4.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not more than 4.0%;

the total area of any such peaks is not more than 5.0%.

Disregard any peak due to the solvent or with an area less than 2.0%.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 10 IU per µg peptide.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection in *water* to give a final concentration of 0.0004 % w/v of the peptide.

(2) 0.0004% w/v of *desmopressin BPCRS* in *water*.

(3) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 2 mL of *water*.

www.webofpharma.com

https://thuathuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12 cm x 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

20 volumes of *acetonitrile for chromatography* and 80 volumes of *0.067 M mixed phosphate buffer solution, pH 7.0*.

The retention time of desmopressin is about 5 minutes; if necessary adjust the concentration of *acetonitrile* in the mobile phase to obtain a retention time of about 5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks at least 2.8.

DETERMINATION OF CONTENT

Calculate the content of $C_{46}H_{64}N_{14}O_{12}S_2$ in the injection from the chromatograms obtained and from the declared content of $C_{46}H_{64}N_{14}O_{12}S_2$ in *desmopressin BPCRS*.

STORAGE

Desmopressin Injection should be protected from light and stored at a temperature of 2° to 8°.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desmopressin Intranasal Solution

General Notices

Action and use

Vasopressin analogue; treatment of diabetes insipidus.

DEFINITION

Desmopressin Intranasal Solution is a solution of Desmopressin containing suitable buffering agents and preservatives.

The intranasal solution complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of desmopressin, $C_{46}H_{64}N_{14}O_{12}S_2$

90.0 to 110.0% of the stated amount of the peptide.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*.

(1) Dilute a volume of the intranasal solution in *water* to produce a solution containing 0.0025% w/v of the peptide.

(2) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 2 mL of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A *0.067M mixed phosphate buffer solution, pH 7.0*.

Mobile phase B 10 volumes of *acetonitrile for chromatography* and 10 volumes of mobile phase A.

Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0-4	76	24	isocratic
4-18	76→58	24→42	linear gradient
18-35	58→48	42→52	linear gradient
35-40	48→76	52→24	linear gradient
40-50	76	24	re-equilibration

Using the prescribed conditions the retention time of [4- L -glutamic acid]desmopressin is about 14 minutes and the retention time of desmopressin is about 15 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 3.4;

the peak due to desmopressin is clearly separated from the peak due to the antimicrobial preservative stated on the label.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not more than 4.0%.

the total area of any such peaks is not more than 5.0%.

Disregard any peak due to the solvent, any antimicrobial preservative stated on the label and any peak with an area less than 0.3%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the intranasal solution in *water* to produce a solution containing 0.0025% w/v of the peptide.

(2) 0.0025% w/v of *desmopressin BPCRS* in *water*.

(3) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 2 mL of *water*.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

A mixture of 2 volumes of *acetonitrile for chromatography* and 8 volumes of *0.067M mixed phosphate buffer solution, pH 7.0*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.8;

the peak due to desmopressin is clearly separated from the peak due to the antimicrobial preservative stated on the label.

The retention time of desmopressin is about 5 minutes. If necessary adjust the concentration of *acetonitrile* in the mobile phase to obtain the correct retention time and *resolution*.

DETERMINATION OF CONTENT

Calculate the content of $C_{46}H_{64}N_{14}O_{12}S_2$ in the intranasal solution from the chromatograms obtained and from the declared content of $C_{46}H_{64}N_{14}O_{12}S_2$ in *desmopressin BPCRS*.

STORAGE

Desmopressin Intranasal Solution should be protected from light and stored at a temperature of 2° to 8°, unless otherwise justified and authorised.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desmopressin Nasal Spray

General Notices

Action and use

Vasopressin analogue; treatment of diabetes insipidus.

DEFINITION

Desmopressin Nasal Spray is a solution of Desmopressin containing suitable buffering agents and preservatives in a suitable container.

The nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of desmopressin, $C_{46}H_{64}N_{14}O_{12}S_2$

90.0 to 110.0% of the stated amount of the peptide.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*.

(1) If necessary dilute a volume of the nasal spray in a solution of 0.9% w/v of *sodium chloride* to produce a solution containing 0.01 to 0.015 % w/v of the peptide.

(2) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 1 mL of a solution of 0.9% w/v *sodium chloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A *0.067M mixed phosphate buffer solution, pH 7.0.*

Mobile phase B *acetonitrile for chromatography*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-16	83	17	isocratic
16-38	83→72	17→28	linear gradient
38-46	72	28	isocratic
46-50	72→83	28→17	linear gradient
50-60	83	17	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 2.0;

the peak due to desmopressin is clearly separated from any peaks due to the excipients stated on the label.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not more than 4.0%;

the total area of any such peaks is not more than 5.0%.

Disregard any peak due to the solvent, any antimicrobial preservative stated on the label and any peak with an area less than 0.3%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) If necessary dilute a volume of the nasal spray in a solution of 0.9% w/v of *sodium chloride* to give a final concentration in the range of 0.01 to 0.015 % w/v of the peptide.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dissolve the contents of a vial of *desmopressin BPCRS* in a solution of 0.9% *sodium chloride* to give a final concentration of 0.01% w/v of the peptide.

(3) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 1 mL of a solution of 0.9% w/v *sodium chloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm). (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

17 volumes of *acetonitrile* and 83 volumes of *0.067M mixed phosphate buffer solution, pH 7.0*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0;

the peak due to desmopressin is clearly separated from any peaks due to the excipients stated on the label.

DETERMINATION OF CONTENT

Calculate the content of $C_{46}H_{64}N_{14}O_{12}S_2$ in the nasal spray from the chromatograms obtained and from the declared content of $C_{46}H_{64}N_{14}O_{12}S_2$ in *desmopressin BPCRS*.

STORAGE

Desmopressin Nasal Spray should be protected from light and stored at a temperature of 2° to 8°, unless otherwise justified and authorised.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Desmopressin.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desmopressin Oral Lyophilisate

General Notices

Action and use

Vasopressin analogue; treatment of diabetes insipidus.

DEFINITION

Desmopressin Oral Lyophilisate contains Desmopressin with suitable excipients.

The oral lyophilisate complies with the requirements stated under Tablets and with the following requirements.

Content of desmopressin, $C_{46}H_{64}N_{14}O_{12}S_2$

90.0 to 110.0% of the stated amount of the peptide.

IDENTIFICATION

In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*.

(1) Shake a quantity of the oral lyophilisate with 10 mL of a mixture of 50% of the buffer solution and 50% of *water* to produce a solution containing 0.0025% w/v of the peptide.
(2) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 4 mL of a mixture of 50% of the buffer solution and 50% of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 3.0 mm) packed with nitrile groups chemically bonded to porous silica particles (5 µm) (Zorbax-SB-CN is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 200 µL of each solution.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Buffer solution

0.05 M ammonium acetate buffer solution, pH 4.6, if necessary adjusted with acetic acid.

Mobile phase A

15 volumes of *acetonitrile*, 35 volumes of *water* and 50 volumes of the Buffer solution.

Mobile phase B

15 volumes of *water*, 40 volumes of *acetonitrile* and 45 volumes of the Buffer solution.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-16	100	0	isocratic
16-31	100→0	0→100	linear gradient
31-36	0	100	isocratic
36-37	0→100	100→0	linear gradient
37-41	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time for the first peak: in solution (2) is about 9 minutes and about 11 minutes for desmopressin.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 2.0;

the peak due to desmopressin is clearly separated from any peaks due to excipients stated on the label.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not more than 2.0%;

the total area of any such peaks is not more than 4.0%.

Disregard any peak due to the solvent, any excipients stated on the label and any peak with an area less than 0.05%.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuvienthuocngocanh.com/

(1) Shake a suitable quantity of the oral lyophilisate with 10 mLof a mixture of 50% of the Buffer solution and 50% of *water*, to give a final concentration of 0.0025% w/v of the peptide.

(2) Dissolve the contents of a vial of *desmopressin BPCRS* in a mixture of 50% of the Buffer solution and 50% of *water*. to give a final concentration of 0.0025% w/v of the peptide.

(3) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 4 mL of a mixture of 50% of the Buffer solution and 50% of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 3.0 mm) packed with nitrile groups chemically bonded to porous silica particles (5 µm) (Zorbax-SB-CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

Carry out isocratic elution for at least 16 minutes for each run.

MOBILE PHASE

Buffer solution 0.05M ammonium acetate buffer solution, pH 4.6, 15 volumes of *acetonitrile*, 35 volumes of *water* and 50 volumes of the Buffer solution.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks and desmopressin is at least 2.0;

the peak due to desmopressin is clearly separated from any peaks due to excipients stated on the label.

DETERMINATION OF CONTENT

Calculate the content of $C_{46}H_{64}N_{14}O_{12}S_2$ in each tablet from the chromatograms obtained and from the declared content of $C_{46}H_{64}N_{14}O_{12}S_2$ in *desmopressin BPCRS*.

STORAGE

Desmopressin Oral Lyophilisate should be protected from light and moisture.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Desmopressin.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desmopressin Tablets

General Notices

Action and use

Vasopressin analogue; treatment of diabetes insipidus; nocturnal enuresis.

DEFINITION

Desmopressin Tablets contain Desmopressin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of desmopressin, $C_{46}H_{64}N_{14}O_{12}S_2$

90.0 to 110.0% of the stated amount of the peptide.

IDENTIFICATION

In the test for Uniformity of content, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 500 mL of *water* as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw a 20 mL sample of the medium and filter.

(2) Prepare a solution of *desmopressin BPCRS* in *water* with a final concentration equal to that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Uniformity of content may be used.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of desmopressin $C_{46}H_{64}N_{14}O_{12}S_2$, in the medium using the declared content of $C_{46}H_{64}N_{14}O_{12}S_2$ in *desmopressin BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and the *normalisation procedure*:

(1) Shake a quantity of powdered tablets containing 0.5 mg with 1 mL of *water* to give a final concentration of 0.05% w/v of the peptide.

(2) Dissolve the contents of a vial of *desmopressin impurity standard BPCRS* in 0.5 mL of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12 cm x 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A *0.067M mixed* *phosphate buffer solution pH 7.0*.

Mobile phase B 10 volumes of *acetonitrile for chromatography* and 10 volumes of mobile phase A.

Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0-4	76	24	isocratic
4-18	76→58	24→42	linear gradient
18-35	58→48	42→52	linear gradient
35-40	48→76	52→24	linear gradient
40-50	76	24	re-equilibration

The retention time of desmopressin is about 16 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 3.4.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not more than 2.0%;

www.webofpharma.com

https://thuocngocanh.com/

the total area of any such peaks is not more than 4.0%.

Disregard any peak due to the solvent or with a relative amount less than 0.05%.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Desmopressin comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions:

(1) Add sufficient *water* to one tablet to produce a solution containing 0.01% w/v of Desmopressin.

(2) 0.01% w/v of *desmopressin BPCRS* in *water*.

(3) Dissolve the contents of a vial *desmopressin impurity standard BPCRS* in 0.5 mL of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12 cm x 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 ml per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 50 µl of each solution.

MOBILE PHASE

2 volumes of *acetonitrile for chromatography* and 8 volumes of *0.067M mixed phosphate buffer solution pH 7.0*.

The retention time of desmopressin is about 5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks at least 2.8.

DETERMINATION OF CONTENT

Calculate the content of $C_{46}H_{64}N_{14}O_{12}S_2$ in each tablet from the chromatograms obtained and from the declared content of $C_{46}H_{64}N_{14}O_{12}S_2$ in *desmopressin BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

Desmopressin Tablets should be protected from moisture.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

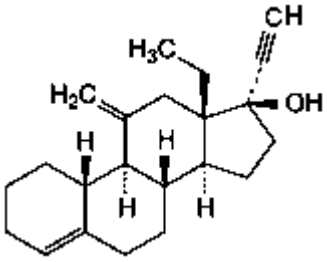
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desogestrel

General Notices

(Ph. Eur. monograph 1717)



$C_{22}H_{30}O$ 310.5 *54024-22-5*

Action and use

Progestogen.

Preparation

Desogestrel Tablets

Ph Eur

DEFINITION

13-Ethyl-11-methylidene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in methanol, freely soluble in anhydrous ethanol and in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison desogestrel CRS.

B. Specific optical rotation (see Tests).

TESTS

Specific optical rotation (2.2.7)

+ 53 to + 57 (dried substance).

Dissolve 0.250 g in anhydrous ethanol R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in 25 mL of acetonitrile R1 and dilute to 50.0 mL with water R.

Reference solution (a) Dissolve 4 mg of desogestrel for system suitability CRS (containing impurities A, B, C and D) in 5 mL of acetonitrile R1 and dilute to 10.0 mL with water R.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of equal volumes of acetonitrile R1 and water R.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with a mixture of equal volumes of acetonitrile R1 and water R.

Reference solution (d) Dissolve 20.0 mg of desogestrel CRS in 25 mL of acetonitrile R1 and dilute to 50.0 mL with water R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: sterically protected octadecylsilyl silica gel for chromatography R (5 µm),

— *temperature*: 50 °C.

Mobile phase water R, acetonitrile R1 (27:73 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 15 µL of the test solution and reference solutions (a), (b) and (c).

Run time 2.5 times the retention time of desogestrel.

Identification of impurities Use the chromatogram supplied with desogestrel for system suitability CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and D.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to desogestrel (retention time = about 22 min): impurity E = about 0.2; impurity D = about 0.25; impurity B = about 0.7; impurity A = about 0.95; impurity C = about 1.05.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to desogestrel.

Limits:

— *correction factors*: for the calculation of content, multiply the peak area of the following impurities by the corresponding correction factor: impurity A = 1.8, impurity D = 1.5;

— *impurities A, B, C*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at a pressure not exceeding 2 kPa.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (d).

Calculate the percentage content of $C_{22}H_{30}O$ from the areas of the peaks and the declared content of *desogestrel CRS*.

IMPURITIES

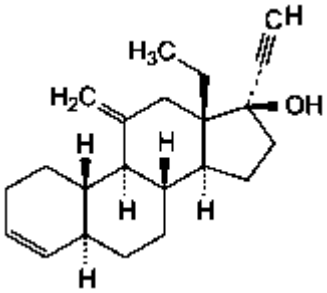
Specified impurities *A, B, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

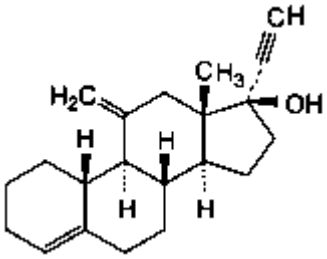
www.webofpharma.com

https://thuocngocanh.com/

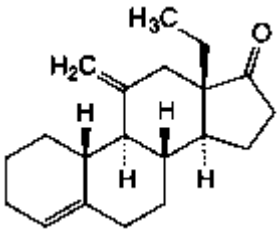
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) E.



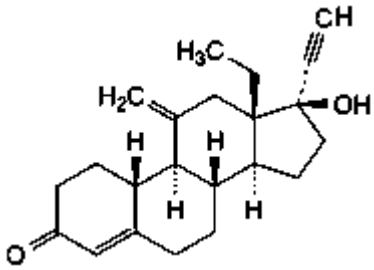
A. 13-ethyl-11-methylidene-18,19-dinor-5α,17α-pregn-3-en-20-yn-17-ol (desogestrel Δ^3-isomer),



B. 11-methylidene-19-nor-17α-pregn-4-en-20-yn-17-ol,



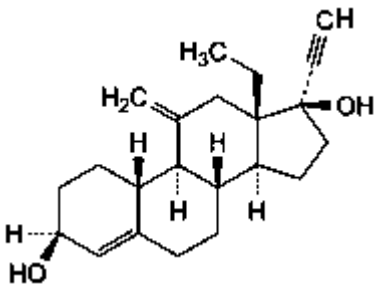
C. 13-ethyl-11-methylidenegon-4-en-17-one,



D. 13-ethyl-17-hydroxy-11-methylidene-18,19-dinor-17α-pregn-4-en-20-yn-3-one,

www.webofpharma.com

https://thuocngocanh.com/



E. 13-ethyl-11-methylidene-18,19-dinor-17α-pregn-4-en-20-yne-3β,17-diol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Desogestrel Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Desogestrel Tablets contain Desogestrel.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of desogestrel, $C_{22}H_{30}O$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *dichloromethane*.

(1) Disperse a quantity of powdered tablets containing 0.75 mg of Desogestrel in 8 mL of *dichloromethane*, mix with the aid of ultrasound and dilute to 10 mL with *dichloromethane* and filter.

(2) 0.0075% w/v of *desogestrel BPCRS*.

(3) 0.0075% w/v each of *desogestrel BPCRS* and *lynestrenol BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel 60 precoated plate for high performance thin-layer chromatography (Merck silica gel 60 HPTLC plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 2 µL of each solution.

(d) After removal of the plate, dry in air, spray it with *ethanolic sulfuric acid (2%)*, heat at 110° for 10 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

A mixture of 20 volumes of *ethyl acetate* and 80 volumes of *toluene*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuathuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) is similar in colour, position and size to the principal spot in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of a 0.3% w/v solution of *sodium lauryl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with a 0.3% w/v solution of *sodium lauryl sulfate* if necessary, expected to contain 0.000015% w/v of Desogestrel.

(2) 0.000015% w/v of *desogestrel BPCRS* in a mixture of 1 volume of *propan-2-ol* and 99 volumes of a 0.3% w/v solution of *sodium lauryl sulfate*.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography R* (5 µm) (Zorbax ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

5 volumes of *water* and 95 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}O$ in the medium from the chromatograms obtained and using the declared content of $C_{22}H_{30}O$ in *desogestrel BPCRS*.

LIMITS

The amount of desogestrel released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 20 volumes of *water* and 80 volumes of *acetonitrile* (Solution A).

www.webofpharma.com

https://thuocngocanh.com/

(1) Disperse a quantity of powdered tablets containing 0.75 mg of Desogestrel in 15 mL of solution A, mix with the aid of ultrasound and dilute with sufficient solution A to produce 20 mL, mix and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and further dilute 2 mL of this solution to 10 mL with solution A.

(3) 0.00375% w/v of *desogestrel BPCRS*, 0.000075% w/v of *desogestrel impurity D BPCRS* and 0.0000375% w/v of *desogestrel impurity E BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography R* (5 µm) (Zorbax ODS is suitable).

(b) Use a gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use detection wavelengths of 230 nm and 210 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A *acetonitrile*.

Mobile phase B 50 volumes of *acetonitrile* and 50 volumes of *water*.

Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0-4.5	0	100	isocratic
4.5-4.6	0→100	100→0	linear gradient
4.6-10.7	100	0	isocratic
10.7-10.8	100→0	0→100	linear gradient
10.8-14	0	100	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), at 210 nm the *resolution* between the peaks due to desogestrel impurity E and desogestrel impurity D is at least 1.5 and the retention time of desogestrel impurity D is not greater than 6 minutes.

LIMITS

In the chromatogram obtained with solution (1) at 210 nm:

the area of any peak due to desogestrel impurity E is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (1%);

the area of any other peak other than the principal peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

In the chromatogram obtained with solution (1) at 230 nm:

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak due to desogestrel impurity D is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (2%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Desogestrel comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 20 volumes of *water* and 80 volumes of *acetonitrile* (Solution A).

(1) To one tablet add 5 mL of solution A, mix with the aid of ultrasound and add sufficient solution A to produce a solution expected to contain 0.00075% w/v of Desogestrel.
(2) 0.00075% w/v of *desogestrel BPCRS*.
(3) 0.00075% w/v of *desogestrel BPCRS*, 0.000015% w/v of *desogestrel impurity D BPCRS* and 0.0000075% w/v of *desogestrel impurity E BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used with the following amendments:

(a) Use a detection wavelength of 210 nm.
(b) Inject 125 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to desogestrel impurity D and desogestrel is at least 1.5 and the retention time of desogestrel impurity D is not greater than 6 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}O$ in the tablets using the declared content of $C_{22}H_{30}O$ in *desogestrel BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Desogestrel

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w of Desogestrel

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 20 volumes of *water* and 80 volumes of *acetonitrile* (Solution A).

(1) To a quantity of powdered tablets containing 0.75 mg of Desogestrel add 10 mL of solution A, mix with the aid of ultrasound and add sufficient solution A to produce 20 mL.
(2) 0.00375% w/v of *desogestrel BPCRS*.
(3) 0.00375% w/v of *desogestrel BPCRS*, 0.000075% w/v of *desogestrel impurity D BPCRS* and 0.0000375% w/v of *desogestrel impurity E BPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic procedure described under Related substances may be used with a detection wavelength of 210 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to desogestrel impurity D and desogestrel is at least 1.5 and the retention time of desogestrel impurity D is not greater than 6 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{30}O$ in the tablets using the declared content of $C_{22}H_{30}O$ in *desogestrel BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities D and E listed under Desogestrel.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

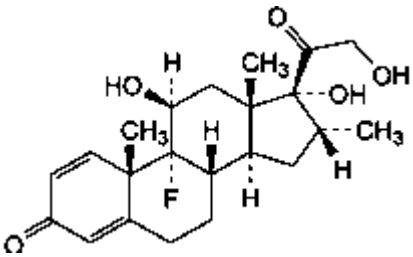
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Dexamethasone

General Notices

(Ph. Eur. monograph 0388)



$C_{22}H_{29}FO_5$ 392.5 *50-02-2*

Action and use

Glucocorticoid.

Preparations

Dexamethasone Eye Drops, Suspension

Dexamethasone and Neomycin Ear Spray

Dexamethasone Tablets

Tobramycin and Dexamethasone Eye Drops, Suspension

Ph Eur

DEFINITION

9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in anhydrous ethanol, slightly soluble in methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *dexamethasone CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *dexamethasone CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a faint reddish-brown colour develops. Add this solution to 10 mL of *water R* and mix; the colour is discharged.

TESTS

Specific optical rotation (*2.2.7*)

+ 86 to + 92 (dried substance).

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Test solution Dissolve 25.0 mg of the substance to be examined in 1.5 mL of acetonitrile R and add 5 mL of mobile phase A. Sonicate until dissolution is complete and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of dexamethasone for system suitability CRS (containing impurities B, F and G) in 0.5 mL of acetonitrile R and add 1 mL of mobile phase A. Sonicate until dissolution is complete and dilute to 2 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of dexamethasone for peak identification CRS (containing impurities J and K) in 0.5 mL of acetonitrile R and add 1 mL of mobile phase A. Sonicate until dissolution is complete and dilute to 2 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: mix 250 mL of acetonitrile R and 700 mL of water for chromatography R and allow to equilibrate; dilute to 1000 mL with water for chromatography R and mix;

— *mobile phase B*: acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 40	100 → 0	0 → 100

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL; inject mobile phase A as a blank.

Identification of impurities Use the chromatogram supplied with dexamethasone for system suitability CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B, F and G; use the chromatogram supplied with dexamethasone for peak identification CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities J and K.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to dexamethasone (retention time = about 15 min): impurity J = about 0.90; impurity B = about 0.94; impurity K = about 1.3; impurity F = about 1.5; impurity G = about 1.7.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to dexamethasone.

Limits:

— *impurity G*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities B, F, J, K*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.100 g in ethanol (96 per cent) R and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with ethanol (96 per cent) R. Measure the absorbance (2.2.25) at the absorption maximum at 238.5 nm.

Calculate the content of $C_{22}H_{29}FO_5$ taking the specific absorbance to be 394.

STORAGE

Protected from light.

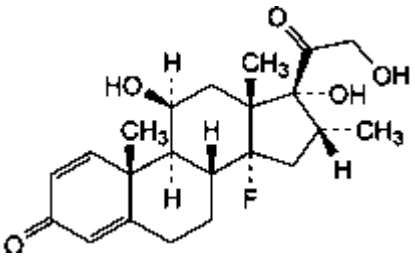
IMPURITIES

Specified impurities *B, F, G, J, K.*

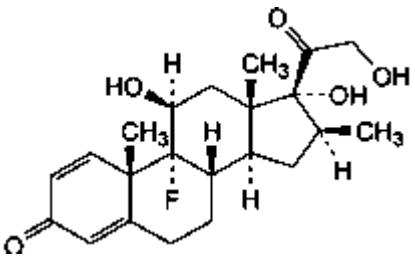
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, H, I.*

www.webofpharma.com

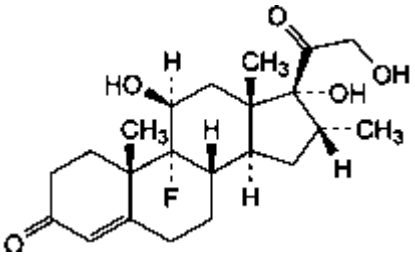
https://thuocngocanh.com/



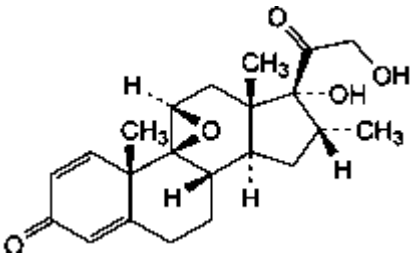
A. 14-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,



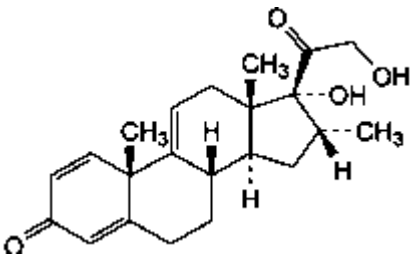
B. 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (betamethasone),



C. 9-fluoro-11β,17,21-trihydroxy-16α-methylpregn-4-ene-3,20-dione,



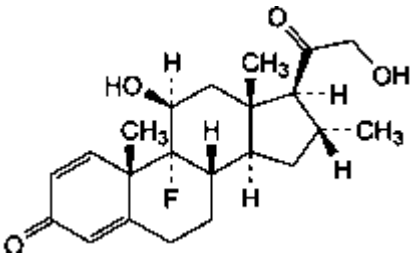
D. 9,11β-epoxy-17,21-dihydroxy-16α-methyl-9β-pregna-1,4-diene-3,20-dione,



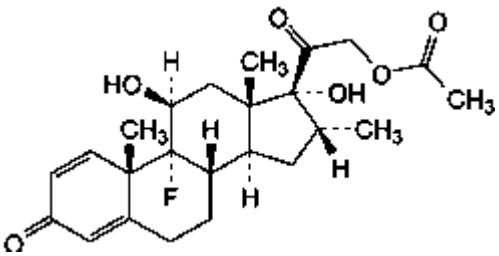
E. 17,21-dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione,

www.webofpharma.com

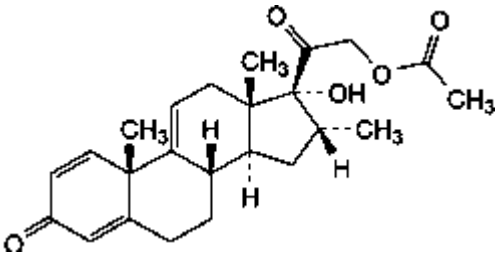
https://thuocngocanh.com/



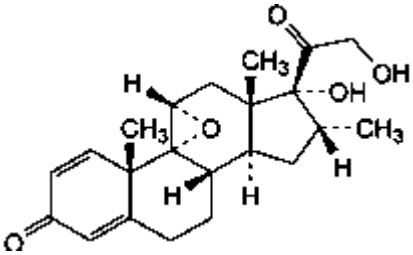
F. 9-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione,



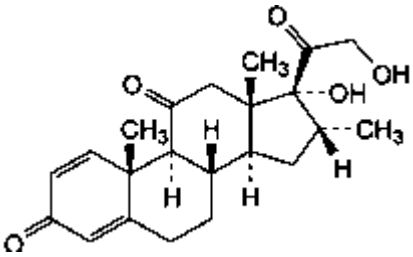
G. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (dexamethasone acetate),



H. 17-hydroxy-16α-methyl-3,20-dioxopregna-1,4,9(11)-trien-21-yl acetate,



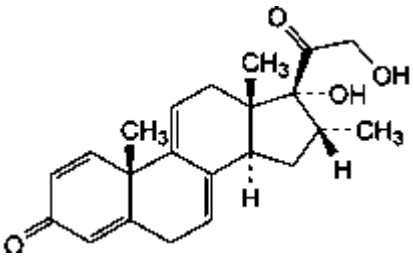
I. 9,11α-epoxy-17,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione,



J. 17,21-dihydroxy-16α-methylpregna-1,4-diene-3,11,20-trione,

www.webofpharma.com

https://thuocngocanh.com/



K. 17,21-dihydroxy-16α-methylpregna-1,4,7,9(11)-tetraene-3,20-dione.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

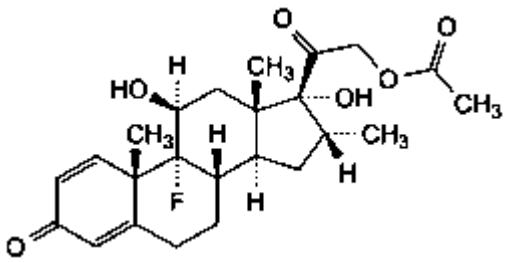
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone Acetate

General Notices

(Ph. Eur. monograph 0548)



$C_{24}H_{31}FO_6$ 434.5 *1177-87-3*

Action and use

Glucocorticoid.

Ph Eur

DEFINITION

9-Fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A, D.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *dexamethasone acetate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution Dissolve 10 mg of *dexamethasone acetate CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *methylene chloride R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a faint reddish-brown colour develops. Add this solution to 10 mL of *water R* and mix. The colour is discharged and a clear solution remains.

D. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (e).

TESTS

Specific optical rotation (2.2.7)

+ 94 to + 99 (dried substance).

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution (a) Dissolve 25.0 mg of the substance to be examined in about 4 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*.

Test solution (b) Dilute 1.0 mL of test solution (a) to 5.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *dexamethasone CRS* (impurity A) and 2 mg of *betamethasone acetate CRS* (impurity D) in the mobile phase, using sonication for about 10 min, and dilute to 100 mL with the mobile phase. Mix 1 mL of this solution and 6 mL of test solution (a) and dilute to 10 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *dexamethasone acetate impurity E CRS* in 1 mL of the mobile phase.

Reference solution (d) Dissolve 5 mg of *dexamethasone acetate for peak identification CRS* (containing impurity I) in about 0.8 mL of *acetonitrile R* and dilute to 2 mL with *water R*.

Reference solution (e) Dissolve 25.0 mg of *dexamethasone acetate CRS* in about 4 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*. Dilute 1.0 mL of the solution to 5.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 380 mL of *acetonitrile R* and 550 mL of *water for chromatography R* and allow to equilibrate; dilute to 1000 mL with *water for chromatography R* and mix.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b), (c) and (d).

Run time 2.5 times the retention time of dexamethasone acetate.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and D; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram supplied with *dexamethasone acetate for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity I.

Relative retention With reference to dexamethasone acetate (retention time = about 22 min): impurity A = about 0.4; impurity D = about 0.9; impurity E = about 1.2; impurity I = about 1.4.

System suitability Reference solution (a):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 3.3 between the peaks due to impurity D and dexamethasone acetate.

Limits:

— *impurity I*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity D*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurities A, E*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase acetonitrile R, water for chromatography R (45:55 *V/V*).

Injection Test solution (b) and reference solution (e).

Run time 1.5 times the retention time of dexamethasone acetate.

Retention time Dexamethasone acetate = about 13 min.

Calculate the percentage content of $C_{24}H_{31}FO_6$ taking into account the assigned content of *dexamethasone acetate CRS*.

STORAGE

Protected from light.

IMPURITIES

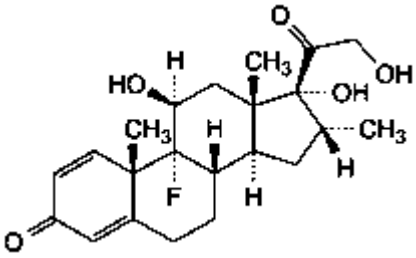
Specified impurities *A, D, E, I*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

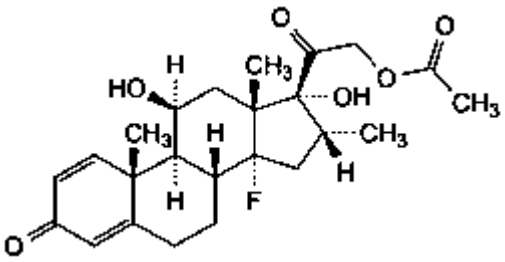
www.webofpharma.com

https://thuocngocanh.com/

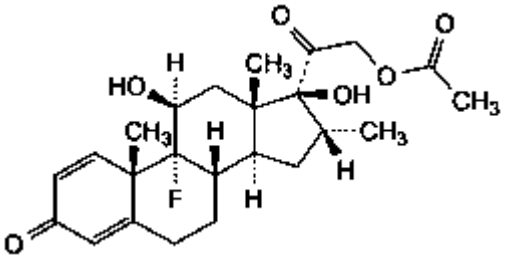
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, F, G, H.



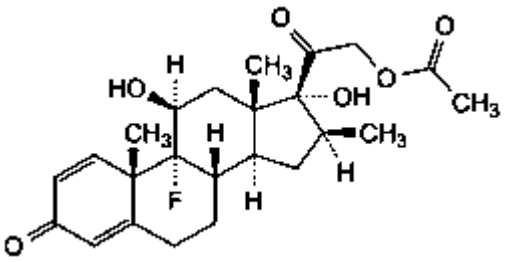
A. 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (dexamethasone),



B. 14-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate,



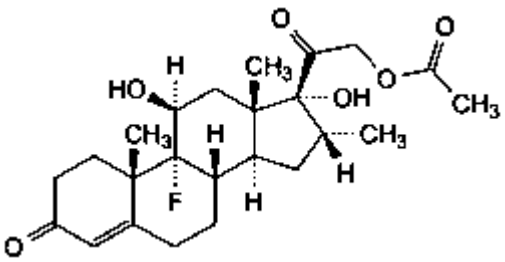
C. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxo-17α-pregna-1,4-dien-21-yl acetate,



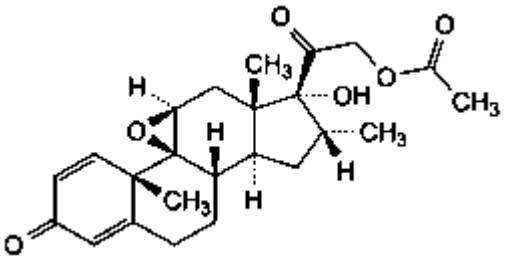
D. 9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (betamethasone acetate),

www.webofpharma.com

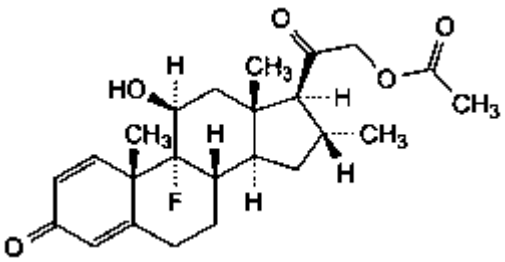
https://thuocngocanh.com/



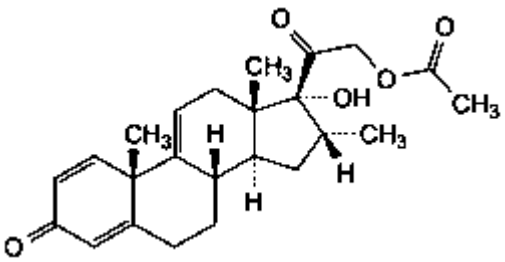
E. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregn-4-en-21-yl acetate,



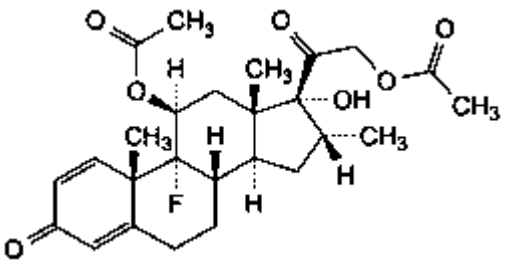
F. 9,11β-epoxy-17-hydroxy-16α-methyl-3,20-dioxo-9β-pregna-1,4-dien-21-yl acetate,



G. 9-fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate,



H. 17-hydroxy-16α-methyl-3,20-dioxopregna-1,4,9(11)-trien-21-yl acetate,



I. 9-fluoro-17-hydroxy-16α-methyl-3,20-dioxopregna-1,4-diene-11β,21-diyl diacetate (dexamethasone 11,21-diacetate).

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone and Neomycin Ear Spray

General Notices

Action and use

Glucocorticoid.

DEFINITION

Dexamethasone and Neomycin Ear Spray is an emulsion containing Dexamethasone in *microfine powder* and Neomycin Sulfate in a suitable vehicle in a suitable metered-dose container. It may contain acetic acid.

The ear spray complies with the requirements stated under Ear Preparations and with the following requirements.

Content of dexamethasone, $C_{22}H_{29}FO_5$

80.0 to 120.0% of the amount stated to be delivered by actuation of the valve.

Shake the ear spray vigorously before carrying out the following tests.

IDENTIFICATION

A. In the Assay for dexamethasone, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Discharge the container a sufficient number of times to obtain a suitable quantity and dilute with *methanol*, if necessary, to produce a solution containing 0.1% w/v of Dexamethasone.

(2) 0.1% w/v of *dexamethasone BPCRS* in *methanol*.

(3) 0.1% w/v of each of *dexamethasone BPCRS* and *betamethasone BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254} plate* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)* (detection method A). Spray with *alcoholic solution of sulfuric acid*. Heat at 120° for 10 minutes or until the spots appear. Allow to cool. Examine the chromatograms in daylight and under *ultraviolet light (365 nm)* (detection method B).

MOBILE PHASE

5 volumes of *butan-2-ol* saturated with *water*, 10 volumes of *toluene* and 85 volumes of *ether*.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two spots which may, however, not be completely separated.

CONFIRMATION

Method A The principal spot in the chromatogram obtained with solution (1) is similar in position and size to the principal spot in the chromatogram obtained with solution (2).

Method B The principal spot in the chromatogram obtained with solution (1) is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with solution (2).

C. In the test for Neomycin C, the principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to the principal spot in the chromatogram obtained with solution (4).
Dexamethasone and Neomycin Ear Spray containing acetic acid complies with the following additional test.

D. Discharge the container a sufficient number of times to produce 0.2 g. The solution yields reaction A characteristic of *acetates*, Appendix VI.

TESTS

Acidity

pH, 2.0 to 3.0, Appendix V L.

Neamine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Discharge the container a sufficient number of times to obtain a suitable quantity (0.5% w/w of neomycin sulfate is suitable).
(2) 0.01% w/v of *neamine EPCRS* in *water*.
(3) Mix 1 volume of solution (1) and 1 volume of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate*.
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution, as 5-mm bands.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry it at 100° to 105° for 10 minutes, spray with *ninhydrin and stannous chloride reagent*, heat at 110° for 15 minutes, spray with the same reagent and heat at 110° for 15 minutes.

MOBILE PHASE

10 volumes of *dichloromethane*, 20 volumes of 13.5M *ammonia* and 30 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1) any spot corresponding to neamine is not more intense than the spot in the chromatogram obtained with solution (2) (2%).

Neomycin C

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Discharge the container a sufficient number of times to obtain a suitable quantity (0.5% w/w of neomycin sulfate is suitable).

(2) 0.075% w/v of *framycetin sulfate EPCRS* in *water*.

(3) Dilute 1 volume of solution (2) to 5 volumes with *water*.

(4) 0.5% w/v of *neomycin sulfate EPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution, as 5-mm bands.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it at 100° to 105° for 10 minutes, spray with *ninhydrin solution R1* and heat at 100° to 105° for 10 minutes.

MOBILE PHASE

20 volumes of *methanol* and 80 volumes of a 20% w/v solution of *sodium chloride*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), a spot appears with an Rf value slightly less than that of the principal spot.

LIMITS

In the chromatogram obtained with solution (1) the spot with an Rf value slightly less than that of the principal spot (neomycin C) is not more intense than the spot in the chromatogram obtained with solution (2) (15%) but is more intense than the spot in the chromatogram obtained with solution (3) (3%).

Related substances

Dexamethasone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After priming the pump, discharge the container a sufficient number of times to obtain 2.5 mg of Dexamethasone, add 1.5 mL of *acetonitrile R* and 5 mL of mobile phase A. Mix with the aid of ultrasound, add sufficient mobile phase A to produce 10 mL and filter through a 0.45-µm filter.

(2) Dilute 1 mL of solution (1) to 100 mL with mobile phase A.

(3) 0.002% w/v of each of *methylprednisolone BPCRS* and *dexamethasone BPCRS* in mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

(4) Dilute 1 mL of solution (2) to 20 mL with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 25% v/v *acetonitrile*.

Mobile phase B *acetonitrile*.

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
0	100	0	isocratic
15	100→0	0→100	begin linear gradient
40	0	100	end chromatogram, return to 100 A
41	100	0	begin equilibration with A
46 = 0	100	0	end equilibration, begin next chromatogram

When the chromatograms are recorded under the prescribed conditions, the retention times are: methylprednisolone, about 12 minutes; dexamethasone, about 14 minutes.

SYSTEM SUITABILITY

The test is not valid unless:

(a) in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to methylprednisolone and dexamethasone is at least 1.5 (if necessary, adjust the concentration of *acetonitrile* in mobile phase A);

(b) in the chromatogram obtained with solution (4), the *signal to noise ratio* of the peak due to dexamethasone is at least 10.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak due to mobile phase A and any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (4) (0.05%).

ASSAY

For dexamethasone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) After priming the pump, discharge the container a sufficient number of times to obtain 1 mg of Dexamethasone, add 10 mL of *methanol*, place in an ultrasonic bath for 10 minutes, cool, dilute to 25 mL with *water*, mix and filter through a 0.45-µm PTFE filter.
(2) Dilute 10 volumes of a 0.010% w/v solution of *dexamethasone BPCRS* in *methanol* to 25 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mix 10 volumes of *glacial acetic acid*, 350 volumes of *acetonitrile* and 640 volumes of *water* and filter (Whatman GF/F is suitable).

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the ear spray using the declared content of $C_{22}H_{29}FO_5$ in *dexamethasone BPCRS*

For neomycin sulfate

Prime the pump and discharge the container a sufficient number of times to obtain a quantity of the emulsion containing 3250 IU; dilute to 50 mL with *sterile* *phosphate buffer pH 8.0*. Dilute 10 mL of the resulting solution to 100 mL with the same solvent and carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU per mL.

STORAGE

Dexamethasone and Neomycin Ear Spray should not be allowed to freeze.

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

The strength with respect to Neomycin Sulfate is stated as the number of IU (Units) per mL.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone Eye Drops, Suspension

General Notices

Action and use

Glucocorticoid.

DEFINITION

Dexamethasone Eye Drops, Suspension are a sterile suspension of Dexamethasone in a suitable vehicle.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of dexamethasone, $C_{22}H_{29}FO_5$

95.0 to 105.0% of the stated amount.

The eye drops should be shaken vigorously before carrying out the following tests.

IDENTIFICATION

Mix a quantity of the Eye drops containing 20 mg of Dexamethasone with 5 mL of 0.1M *sodium hydroxide*, add 50 mL of *dichloromethane* and mix with the aid of ultrasound for 20 minutes, filter the dichloromethane layer and evaporate to dryness using a rotary evaporator. Dry the residue at 105° for 2 hours. The *infrared absorption* spectrum of the dried residue, Appendix II A, is concordant with the *reference spectrum* of dexamethasone *(RS 089)*.

TESTS

Particle size

The eye drops are a suspension and comply with the following test:

Examine using an automated light obscuration instrument such as that described in Appendix XIII A. Not more than 20 particles greater than 25 µm, not more than 2 particles greater than 50 µm and no particles greater than 90 µm.

Acidity

pH, 5.0 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

(1) Disperse a quantity of the eye drops containing 20 mg of Dexamethasone in 70 mL of mobile phase, mix with the aid of ultrasound for 10 minutes, dilute with sufficient mobile phase to produce 100 mL and filter.

(2) Dilute 3 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.02% w/v of *dexamethasone impurity standard BPCRS*.

(4) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase, dilute 1 mL of this solution to 10 volumes with mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography R* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for six times the retention time of dexamethasone.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of a 0.3% w/v solution of *orthophosphoric acid* that has been previously adjusted to pH 3.0 with *dilute sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to impurity 3 and dexamethasone is at least 1.5;

closely resembles the chromatogram supplied with *dexamethasone impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks, apart from the principal peak, is not greater than the area of the peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the area of the peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Disperse a quantity of the eye drops containing 20 mg of Dexamethasone in 70 mL of mobile phase, mix with the aid of ultrasound for 10 minutes, dilute with sufficient mobile phase to produce 100 mL and filter.

(2) 0.02% w/v of *dexamethasone BPCRS*.

(3) 0.01% w/v of *dexamethasone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to impurity 3 and dexamethasone is at least 1.5;

closely resembles the chromatogram supplied with *dexamethasone impurity standard BPCRS*.

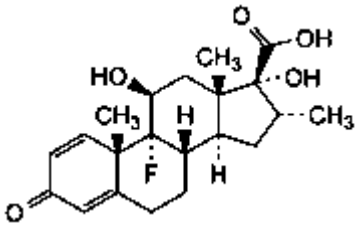
DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the eye drops using the declared content of $C_{22}H_{29}FO_5$ in *dexamethasone BPCRS*.

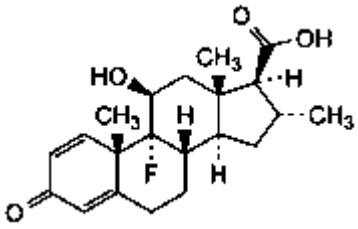
STORAGE

Dexamethasone Eye Drops, Suspension should be stored in accordance with the manufacturer's instructions.

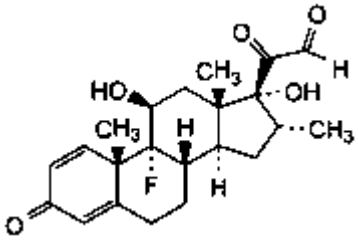
IMPURITIES



1. Dexamethasone-17β-carboxylic acid.



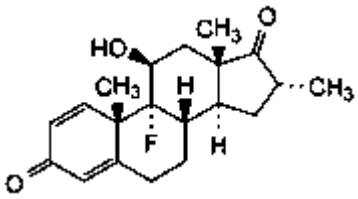
2. Dexamethasone-17α-dehydroxy-17β-carboxylic acid.



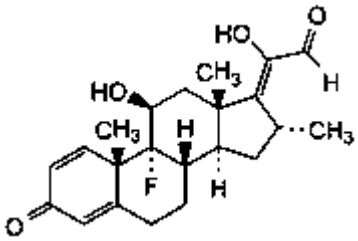
3. Dexamethasone-21-aldehyde.

www.webofpharma.com

https://thuocngocanh.com/



4. Dexamethasone-17-ketone.



5. Dexamethasone-17(20)-enol-21-aldehyde.

© Crown Copyright 2022

www.webofpharma.com

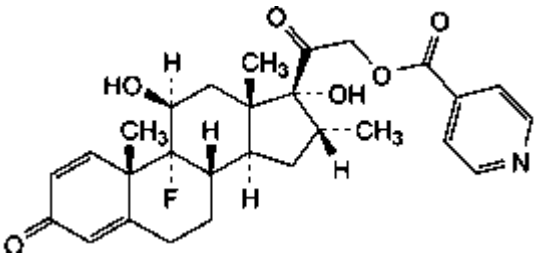
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone Isonicotinate

General Notices

(Ph. Eur. monograph 2237)



$C_{28}H_{32}FNO_6$ 497.6 *2265-64-7*

Action and use

Glucocorticoid.

Ph Eur

DEFINITION

9-Fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl pyridine-4-carboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol and in acetone.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *dexamethasone isonicotinate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Specific optical rotation (2.2.7)

+ 142 to + 146 (dried substance).

Suspend 0.200 g in 4.0 mL of *ethyl acetate R* and dilute to 20.0 mL with *ethanol (96 per cent) R*. Treat in an ultrasonic bath until a clear solution is obtained.

Related substances

Liquid chromatography (2.2.29). *Prepare solutions immediately before use.*

Test solution Suspend 50.0 mg in 7 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*. Treat in an ultrasonic bath until a clear solution is obtained.

Reference solution (a) Suspend 5.0 mg of *dexamethasone CRS* (impurity A) and 5.0 mg of *dexamethasone acetate CRS* (impurity B) in 70 mL of *acetonitrile R*, add 1.0 mL of the test solution and dilute to 100.0 mL with *water R*. Treat in an ultrasonic bath until a clear solution is obtained.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *water R*.

Reference solution (c) Suspend 5 mg of *dexamethasone isonicotinate for impurity C identification CRS* in 0.7 mL of *acetonitrile R* and dilute to 1 mL with *water R*. Treat in an ultrasonic bath until a clear solution is obtained.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm,

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water for chromatography R*,

— *mobile phase B*: *acetonitrile for chromatography R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	68	32
2 - 20	68 → 50	32 → 50

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 240 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B; use the chromatogram supplied with *dexamethasone isonicotinate for impurity C identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to dexamethasone isonicotinate (retention time = about 12 min): impurity A = about 0.4; impurity C = about 0.6; impurity B = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity B and dexamethasone isonicotinate.

Limits:

— *impurity A*: not more than 5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *impurity B*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

— *impurity C*: not more than 3 times the area of the peak due to dexamethasone isonicotinate in the chromatogram obtained with reference solution (b) (0.3 per cent),

— *unspecified impurities*: for each impurity, not more than the area of the peak due to dexamethasone isonicotinate in the chromatogram obtained with reference solution (b) (0.10 per cent),

— *total*: not more than 8 times the area of the peak due to dexamethasone isonicotinate in the chromatogram obtained with reference solution (b) (0.8 per cent),

— *disregard limit*: 0.5 times the area of the peak due to dexamethasone isonicotinate in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C at a pressure not exceeding 0.1 kPa for 4 h.

ASSAY

Dissolve 0.400 g in a mixture of 5 mL of *anhydrous formic acid R* and 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

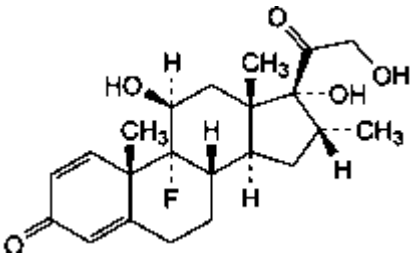
1 mL of *0.1 M perchloric acid* is equivalent to 49.76 mg of $C_{28}H_{32}FNO_6$.

IMPURITIES

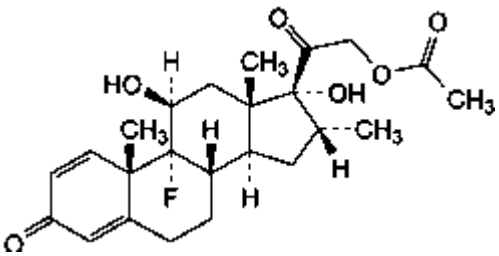
Specified impurities *A, B, C.*

www.webofpharma.com

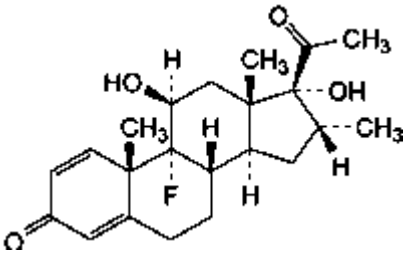
https://thuocngocanh.com/



A. 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (dexamethasone),



B. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (dexamethasone acetate),



C. 9-fluoro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione (21-deoxydexamethasone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

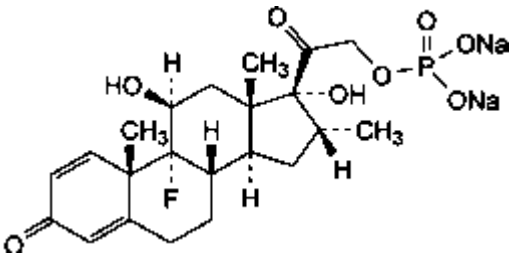
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone Sodium Phosphate

General Notices

(Ph. Eur. monograph 0549)



$C_{22}H_{28}FNa_2O_8P$ 516.4 *2392-39-4*

Action and use

Glucocorticoid.

Preparations

Dexamethasone Sodium Phosphate Eye Drops

Dexamethasone Sodium Phosphate Injection

Dexamethasone Sodium Phosphate Oral Solution

Ph Eur

DEFINITION

Disodium 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl phosphate.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, D.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *dexamethasone sodium phosphate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol (96 per cent) R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 10 mg of *dexamethasone sodium phosphate CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with a solution prepared as follows: dissolve 0.25 g of *2,4-dihydroxybenzaldehyde R* in *glacial acetic acid R*, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of *sulfuric acid R* and 37.5 mL of *glacial acetic acid R*; heat the plate at 90 °C for 35 min or until the spots appear and allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Add about 2 mg to 2 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a faint yellowish-brown colour develops. Add the solution to 10 mL of *water R* and mix. The colour disappears and a clear solution remains.

D. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (b).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

pH (*2.2.3*)

7.5 to 9.5.

Dilute 1 mL of solution S to 5 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

+ 75 to + 83 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solution A Dissolve 7.0 g of *ammonium acetate R* in 1000 mL of *water R*.

Test solution Dissolve 10 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 2 mg of *betamethasone sodium phosphate CRS* (impurity B) and 2 mg of *dexamethasone sodium phosphate CRS* in mobile phase A, then dilute to 100 mL with mobile phase A.

Reference solution (b) Dissolve 2 mg of *dexamethasone sodium phosphate for peak identification CRS* (containing impurities A, C, D, E, F and G) in mobile phase A and dilute to 2 mL with mobile phase A.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: mix 300 mL of solution A and 350 mL of *water for chromatography R*, adjust to pH 3.8 with *acetic acid R*, then add 350 mL of *methanol R*;

— *mobile phase B*: adjust 300 mL of solution A to pH 4.0 with *acetic acid R*, then add 700 mL of *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3.5	90	10
3.5 - 23.5	90 → 60	10 → 40
23.5 - 34.5	60 → 5	40 → 95
34.5 - 50	5	95

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *dexamethasone sodium phosphate for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, C, D, E, F and G; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to dexamethasone sodium phosphate (retention time = about 22 min): impurity C = about 0.5; impurity D = about 0.6; impurity E = about 0.8; impurity F = about 0.92; impurity B = about 0.95; impurity A = about 1.37; impurity G = about 1.41.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity B and dexamethasone sodium phosphate.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.75;

— *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurity G*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities B, C, D, E, F*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Inorganic phosphates

Maximum 1 per cent.

Dissolve 50 mg in *water R* and dilute to 100 mL with the same solvent. To 10 mL of the solution add 5 mL of *molybdovanadic reagent R*, mix and allow to stand for 5 min. Any yellow colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 10 mL of *phosphate standard solution (5 ppm PO_4) R*.

Ethanol (*2.4.24, System A*)

Maximum 1.5 per cent.

Water (*2.5.12*)

Maximum 10.0 per cent, determined on 0.200 g.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *dexamethasone CRS* (impurity A) and 2 mg of *dexamethasone sodium phosphate CRS* in 2 mL of *tetrahydrofuran R*, then dilute to 100 mL with the mobile phase. Dilute 5 mL of this solution to 50 mL with the mobile phase.

Reference solution (b) Dissolve 30.0 mg of *dexamethasone sodium phosphate CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 520 mL of *water for chromatography R* with 2 mL of *phosphoric acid R*. Adjust the temperature to 20 °C, then adjust to pH 2.6 with *sodium hydroxide R*. Mix this solution with 36 mL of *tetrahydrofuran R* and 364 mL of *methanol R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL.

Run time 3 times the retention time of dexamethasone sodium phosphate.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to dexamethasone sodium phosphate (retention time = about 8 min): impurity A = about 2.0.

System suitability Reference solution (a):

— *resolution*: minimum 6.0 between the peaks due to dexamethasone sodium phosphate and impurity A.

Calculate the percentage content of $C_{22}H_{28}FNa_2O_8P$ using the chromatogram obtained with reference solution (b) and taking into account the assigned content of *dexamethasone sodium phosphate CRS*.

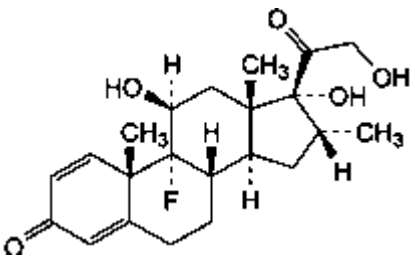
STORAGE

In an airtight container, protected from light.

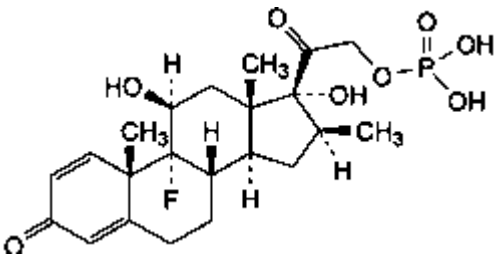
IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H.*



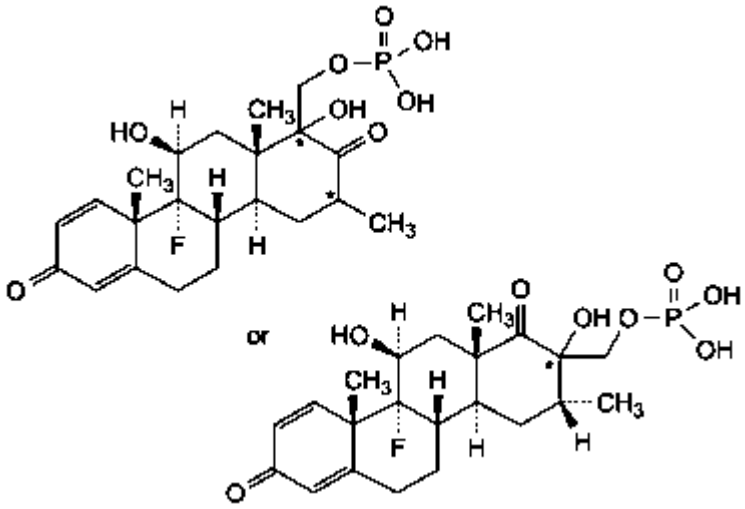
A. 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (dexamethasone),



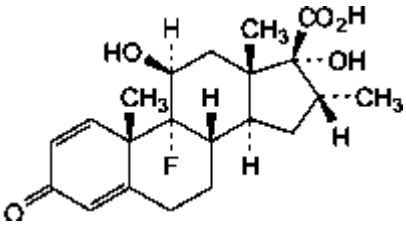
B. 9-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-21-yl dihydrogen phosphate (betamethasone phosphate),

www.webofpharma.com

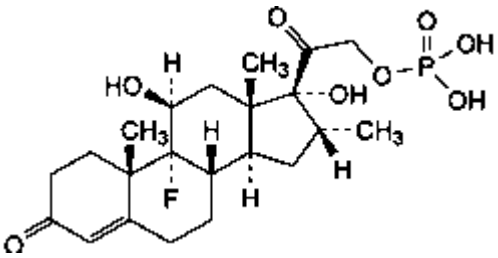
https://thuocngocanh.com/



C, D, E, F. for each impurity: one or more diastereoisomer(s) of (9-fluoro-11β,17aξ-dihydroxy-16ξ-methyl-3,17-dioxo-17aξ-homoandrosta-1,4-dien-17aξ-yl)methyl dihydrogen phosphate (undefined stereochemistry at C-16 and C-17a), or (9-fluoro-11β,17ξ-dihydroxy-16α-methyl-3,17a-dioxo-17a-homoandrosta-1,4-dien-17ξ-yl)methyl dihydrogen phosphate (undefined stereochemistry at C-17),



G. 9-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid,



H. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregn-4-en-21-yl dihydrogen phosphate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone Sodium Phosphate Eye Drops, Solution

General Notices

Action and use

Glucocorticoid.

DEFINITION

Dexamethasone Sodium Phosphate Eye Drops, Solution are a sterile Solution of Dexamethasone Sodium Phosphate in a suitable vehicle.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of dexamethasone sodium phosphate, $C_{22}H_{28}FNa_2O_8P$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the eye drops containing 20 mg of Dexamethasone Sodium Phosphate with 5 mL of 0.1M *sodium hydroxide*, add 50 mL of *dichloromethane* and mix with the aid of ultrasound for 20 minutes, filter the dichloromethane layer and evaporate to dryness using a rotary evaporator. Dry the residue at 105° for 2 hours. The *infrared absorption* spectrum of the dried residue, Appendix II A, is concordant with the *reference spectrum* of dexamethasone *(RS 089)*.

TESTS

Alkalinity

pH, 7.0 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Disperse a quantity of the eye drops containing 20 mg of Dexamethasone Sodium Phosphate in 70 mL, mix with the aid of ultrasound for 10 minutes, dilute to 100 mL and filter.
(2) Dilute 3 volumes of solution (1) to 100 volumes.
(3) 0.02% w/v of *dexamethasone impurity standard BPCRS*.
(4) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of this solution to 10 volumes

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography R* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for six times the retention time of dexamethasone sodium phosphate.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of a 0.3% w/v solution of *orthophosphoric acid* that has been previously adjusted to pH 3.0 with 2M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to impurity 3 and dexamethasone is at least 1.5;

the chromatogram closely resembles the chromatogram supplied with *dexamethasone impurity standard BPCRS*.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* is not greater than the area of the peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the area of the peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Disperse a quantity of the eye drops containing 20 mg of Dexamethasone Sodium Phosphate in 70 mL, mix with the aid of ultrasound for 10 minutes, dilute to 100 mL and filter.

(2) 0.015% w/v of *dexamethasone BPCRS*.

(3) 0.02% w/v of *dexamethasone impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to impurity 3 and dexamethasone is at least 1.5;

the chromatogram closely resembles the chromatogram supplied with *dexamethasone impurity standard BPCRS*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

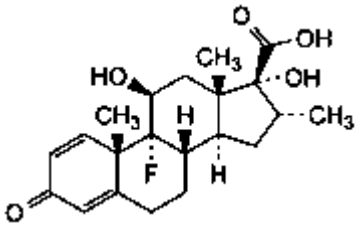
DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{28}FNa_2O_8P$ in the eye drops using the declared content of $C_{22}H_{29}FO_5$ in *dexamethasone BPCRS*. Each mg of $C_{22}H_{29}FO_5$ is equivalent to 1.3157 mg of $C_{22}H_{28}FNa_2O_8P$.

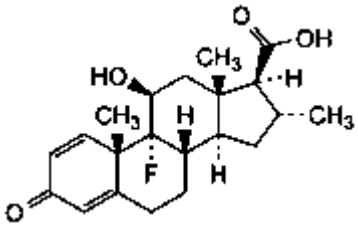
STORAGE

Dexamethasone Sodium Phosphate Eye Drops should be stored in accordance with the manufacturer's instructions.

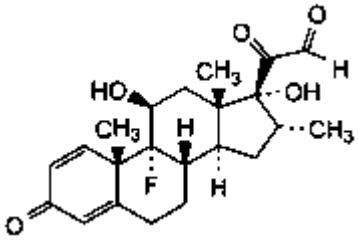
IMPURITIES



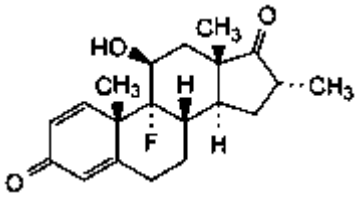
1. dexamethasone-17β-carboxylic acid,



2. dexamethasone-17α-dehydroxy-17β-carboxylic acid,

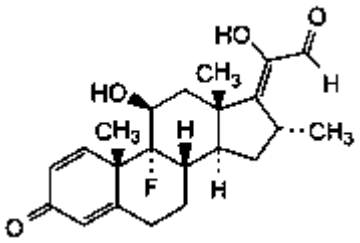


3. dexamethasone-21-aldehyde,



4. dexamethasone-17-ketone,

www.webofpharma.com



5. dexamethasone-17(20)-enol-21-aldehyde.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone Sodium Phosphate Injection

General Notices

Action and use

Glucocorticoid.

DEFINITION

Dexamethasone Sodium Phosphate Injection is a sterile solution of Dexamethasone Sodium Phosphate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of dexamethasone, $C_{22}H_{29}FO_5$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Dilute, if necessary, a volume of the injection to contain the equivalent of 0.08% w/v of dexamethasone.

(2) 0.1% w/v of *dexamethasone sodium phosphate BPCRS*.

(3) 0.1% w/v each of *dexamethasone sodium phosphate BPCRS* and *prednisolone sodium phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, heat at 110° for 10 minutes, spray the hot plate with *ethanolic sulfuric acid (20%)* and heat at 120° for 10 minutes; cool and examine in daylight and under *ultraviolet light (365 nm)*.

MOBILE PHASE

20 volumes of *acetic acid*, 20 volumes of *water* and 60 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless the chromatogram obtained with solution (3) shows two spots which may, however, not be completely separated.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH, 7.0 to 8.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Dilute a volume of the injection to produce a solution containing the equivalent of 0.08% w/v of dexamethasone.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.01% w/v each of *dexamethasone sodium phosphate BPCRS* and *betamethasone sodium phosphate BPCRS*.
(4) 0.1% w/v of *dexamethasone sodium phosphate for peak identification EPCRS*.
(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography R* (5 µm) (Kromasil C8 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), continue the chromatography for twice the retention time of the principal peak.

MOBILE PHASE

Mobile phase A 300 volumes of 0.09M *ammonium acetate* and 350 volumes of water, adjusted to pH 3.8 with *acetic acid*, then add 350 volumes of *methanol*.

Mobile phase B 300 volumes of 0.09M *ammonium acetate*, adjusted to pH 4.0 with *acetic acid*, and 700 volumes of *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3.5	90	10	isocratic
3.50-23.5	90→60	10→40	linear gradient
23.5-34.5	60→5	40→95	linear gradient
34.5-50	5	95	isocratic
50-55	5→90	95→10	linear gradient
55-65	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to dexamethasone sodium phosphate (retention time about 22 minutes) are impurity 1, about 0.1; impurity C, about 0.5; impurity D, about 0.6; impurity E, about 0.8; impurity F, about 0.92; impurity B, about 0.95; impurity A, about 1.37 and impurity G, about 1.41.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to betamethasone sodium phosphate and dexamethasone sodium phosphate is at least 2.0.

LIMITS

Identify any peak corresponding to impurity A in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (4) and multiply the area by a correction factor of 0.75.

In the chromatogram obtained with solution (1):

the areas of any peak corresponding to impurity A, impurity B, impurity C, impurity D, impurity E, impurity F or impurity G are not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

the sum of the areas of any *secondary peaks* is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a volume of the injection to produce a solution containing the equivalent of 0.0066% w/v of dexamethasone.
(2) 0.009% w/v of *dexamethasone sodium phosphate BPCRS*.
(3) 0.002% w/v each of *dexamethasone sodium phosphate BPCRS* and *betamethasone sodium phosphate BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography R* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

To 1.360 g of *potassium dihydrogen phosphate* add 0.600 g of *hexylamine*, mix, allow to stand for 10 minutes, dissolve in 182.5 mL of *water*, add 67.5 mL of *acetonitrile*, mix and filter (0.45 µm).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to betamethasone sodium phosphate and dexamethasone sodium phosphate is at least 2.2.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the injection from the peak areas obtained and from the declared content of $C_{22}H_{28}FNa_2O_8P$ in *dexamethasone sodium phosphate BPCRS*. 1 mg of $C_{22}H_{28}FNa_2O_8P$ is equivalent to 0.760 mg of $C_{22}H_{29}FO_5$.

STORAGE

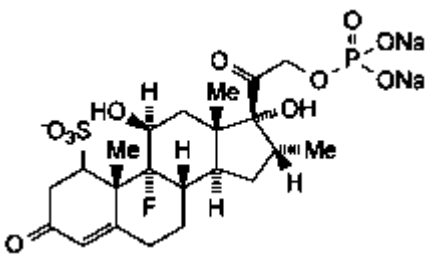
Dexamethasone Sodium Phosphate Injection should be protected from light. It should not be allowed to freeze.

LABELLING

The content of active ingredient is stated as the equivalent amount of dexamethasone in a suitable dose-volume.

IMPURITIES

The impurities limited by the requirements of this monograph those listed under Dexamethasone Sodium Phosphate and:



1. disodium 9-fluoro-11β,17-dihydroxy-16α-methyl-3-oxo-1ζ-sulfopregn-4-ene-21-yl phosphate (Sulfite adduct).

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone Sodium Phosphate Oral Solution

General Notices

Action and use

Glucocorticoid

DEFINITION

Dexamethasone Sodium Phosphate Oral Solution contains Dexamethasone Sodium Phosphate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of dexamethasone sodium phosphate, $C_{22}H_{28}FNa_2O_8P$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the oral solution containing 25 mg of Dexamethasone Sodium Phosphate add sufficient *methanol* to produce 100 mL, centrifuge and use the supernatant liquid.

(2) 0.025% w/v of *dexamethasone sodium phosphate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *water* and 60 volumes of *butanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (40%)*.

(1) To a quantity of the oral solution containing 10 mg of Dexamethasone Sodium Phosphate add sufficient *methanol (40%)* to produce 100 mL and filter.

(2) 0.0001% w/v of *dexamethasone sodium phosphate BPCRS*.

(3) 0.0001% w/v of *betamethasone sodium phosphate BPCRS*.

(4) 0.0025% w/v of each of *dexamethasone BPCRS* and *betamethasone BPCRS*.

(5) Dilute 5 volumes of solution (2) to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 2.0 mm) packed with *octylsilyl silica gel for chromatography* (3 µm) (Luna C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.25 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 39 volumes of *methanol* and 61 volumes of a 0.68% w/v solution of *potassium dihydrogen orthophosphate*; adjust the pH to 3.5 with *dilute orthophosphoric acid* or *dilute sodium hydroxide*.

Mobile phase B 41 volumes of *methanol* and 59 volumes of a 0.68% w/v solution of *potassium dihydrogen orthophosphate*; adjust the pH to 3.5 with *dilute orthophosphoric acid* or *dilute sodium hydroxide*.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0	100	0	isocratic
30→40	100→0	0→100	linear gradient
40→75	0	100	isocratic
75→80	0→100	100→0	linear gradient
80→90	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to dexamethasone and betamethasone is at least 1.5.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to betamethasone sodium phosphate is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the impurities is not greater than 1.0%.

Disregard any peak due to dexamethasone and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

Free dexamethasone

In the Assay, the area of any peak due to dexamethasone in the chromatogram obtained with solution (1) is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (34%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (45%)*.

(1) To a quantity of the oral solution containing the equivalent of 8 mg of Dexamethasone Sodium Phosphate add sufficient *methanol (45%)* to produce 100 mL and filter through a 0.45-µm nylon filter.
(2) 0.008% w/v of *dexamethasone sodium phosphate BPCRS* and 0.0027% w/v of *dexamethasone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

44 volumes of *methanol* and 56 volumes of a 0.68% w/v solution of *potassium dihydrogen orthophosphate*, adjust the pH to 3.5 with *dilute orthophosphoric acid* or *dilute sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to dexamethasone sodium phosphate and dexamethasone is at least 10.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{22}H_{28}FNa_2O_8P$ using the declared content of $C_{22}H_{28}FNa_2O_8P$ in *dexamethasone sodium phosphate BPCRS* and the declared content of $C_{22}H_{29}FO_5$ in *dexamethasone BPCRS*. Each mg of $C_{22}H_{29}FO_5$ is equivalent to 1.3158 mg of $C_{22}H_{28}FNa_2O_8P$.

Calculate the total content of $C_{22}H_{28}FNa_2O_8P$ in the oral solution from the equivalent amount of dexamethasone sodium phosphate due to Free dexamethasone and combining this with the content of dexamethasone sodium phosphate.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamethasone Tablets

General Notices

Action and use

Glucocorticoid.

DEFINITION

Dexamethasone Tablets contain Dexamethasone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dexamethasone, $C_{22}H_{29}FO_5$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Mix a quantity of the powdered tablets containing 20 mg of Dexamethasone with 5 mL of 0.1M *sodium hydroxide*, add 50 mL of *dichloromethane* and mix with the aid of ultrasound for 20 minutes, filter and evaporate to dryness using a rotary evaporator. Dry the residue at 105° for 2 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of dexamethasone *(RS 089)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 2.5 mg of Dexamethasone add 10 mL of *acetonitrile*, mix with the aid of ultrasound and filter through a 0.45-µm filter. Dilute 4 mL of the filtrate to 10 mL with *water*.

(2) Dilute 1 volume of solution (1) to 100 volume with mobile phase A.

(3) 0.002% w/v each of *dexamethasone BPCRS* and *methylprednisolone BPCRS* in mobile phase A.

(4) Dilute 1 volume of solution (2) to 20 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use gradient elution and the mobile phases described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Use a flow rate of 2.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) The retention times are: methylprednisolone about 13 min and dexamethasone about 16 min.

MOBILE PHASE

Mobile phase A 15% v/v *acetonitrile*.

Mobile phase B *acetonitrile*.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0	100	0	isocratic
15	100 → 0	0 → 100	begin linear gradient
40	0	100	end chromatogram, return to 100 A
41	100	0	begin equilibration with A
46 = 0	100	0	end equilibration, begin next chromatogram

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between methylprednisolone and dexamethasone is at least 2.8.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak due to mobile phase A and any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (4) (0.05%).

Uniformity of content

Tablets containing less than 2 mg and or less than 2% w/w of Dexamethasone comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) To one tablet, add sufficient *methanol (50%)* to produce a solution containing 0.0025% w/v of Dexamethasone, shake for 10 minutes and filter through glass-fibre filter (Whatman GF/C is suitable).

(2) 0.0025% w/v of *dexamethasone BPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.4 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

47 volumes of *methanol* *and* 53 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in each tablet using the declared content of $C_{22}H_{29}FO_5$ in *dexamethasone BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Dexamethasone

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w of Dexamethasone

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 2.5 mg of Dexamethasone add 20 mL of *methanol (50%)*, shake for 20 minutes and filter through glass-fibre filter (Whatman GF/C is suitable).

(2) 0.0125% w/v of *dexamethasone BPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_5$ in the tablets using the declared content of $C_{22}H_{29}FO_5$ in *dexamethasone BPCRS*.

STORAGE

Dexamethasone Tablets should be protected from light.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

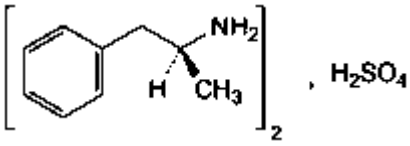
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamfetamine Sulfate

General Notices

(Ph. Eur. monograph 2752)



$C_{18}H_{28}N_2O_4S$ 368.5 *51-63-8*

Action and use

Amfetamine.

Preparation

Dexamfetamine Tablets

Ph Eur

DEFINITION

Bis[(2*S*)-1-phenylpropan-2-amine] sulfate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, B, D.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: C, D.

A. Enantiomeric purity (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dexamfetamine sulfate CRS*.

C. To 50 mL of solution S add 5 mL of *strong sodium hydroxide solution R* and 0.5 mL of *benzoyl chloride R* and shake. Continue to add *benzoyl chloride R* in portions of 0.5 mL, shaking after each addition, until no further precipitate is formed. Filter, wash the precipitate with *water R*, recrystallise twice from a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*, then dry at 100-105 °C. The crystals melt (2.2.14) at 155 °C to 160 °C.

D. Solution S (see Tests) gives reaction (a) of sulfates (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 25 mL of solution S add 0.1 mL of *methyl red solution R*. Not more than 0.1 mL of *0.01 M hydrochloric acid* or *0.01 M sodium hydroxide* is required to change the colour of the indicator.

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in *methanol R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 20.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *amfetamine sulfate CRS* (containing impurity E and dexamfetamine) in 5 mL of *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *vancomycin-bonded silica gel for chiral separation R* (5 µm);

— *temperature*: 25 °C.

Mobile phase *concentrated ammonia R1*, *glacial acetic acid R*, *methanol R2* (0.1:1:998.9 *V/V/V*).

Flow rate 1.0 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 210 nm.

Injection 5 µL.

Run time 1.5 times the retention time of dexamfetamine.

Identification of peaks Use the chromatogram supplied with *amfetamine sulfate CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to dexamfetamine and impurity E.

Relative retention With reference to dexamfetamine (retention time = about 10 min): impurity E = about 1.1.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to dexamfetamine and impurity E.

Calculation of percentage content:

— for impurity E, use the concentration of dexamfetamine sulfate in reference solution (a).

Limit:

— *impurity E*: maximum 5.0 per cent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture Mix 5 mL of *trifluoroacetic acid R* and 900 mL of *water for chromatography R*, adjust to pH 2.2 with *concentrated ammonia R* and dilute to 1000 mL with *acetonitrile R*.

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *1-phenylpropan-2-ol R* (impurity A) and 5 mg of *benzaldehyde R* (impurity D) in the solvent mixture and dilute to 10 mL with the solvent mixture. Dilute 1 mL of the solution to 100 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: solvent mixture;

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	100	0
1 - 16	100 → 65	0 → 35
16 - 21	65 → 0	35 → 100
21 - 23	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 257 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and D.

Relative retention With reference to dexamfetamine (retention time = about 8 min): impurity D = about 1.6; impurity A = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurities D and A.

Calculation of percentage contents:

— for each impurity, use the concentration of dexamfetamine sulfate in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *0.1 M perchloric acid* is equivalent to 36.85 mg of $C_{18}H_{28}N_2O_4S$.

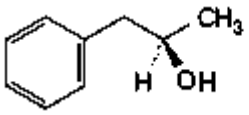
STORAGE

Protected from light.

IMPURITIES

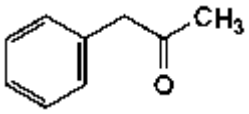
Specified impurities E.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.

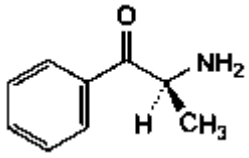


and enantiomer

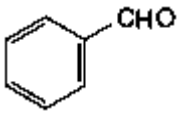
A. (2*RS*)-1-phenylpropan-2-ol,



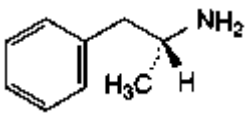
B. 1-phenylpropan-2-one,



C. (2*S*)-2-amino-1-phenylpropan-1-one (cathinone),



D. benzaldehyde,



E. (2*R*)-1-phenylpropan-2-amine (levamfetamine).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexamfetamine Tablets

General Notices

Action and use

Amfetamine.

DEFINITION

Dexamfetamine Tablets contain Dexamfetamine Sulfate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dexamfetamine sulfate, $(C_9H_{13}N)_2,H_2SO_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powdered tablets containing 0.1 g of dexamfetamine sulfate as completely as possible in 20 mL of *water*, filter, add 2 mL of 5M *sodium hydroxide* and extract with three 25 mL quantities of *ether*, washing the combined extracts with 5 mL of *water*. To the ether solution add 10 mL of 0.05M *sulfuric acid* and shake well. The acid layer, after warming to dispel residual ether and cooling to 20°, is dextrorotatory.

B. Extract a quantity of the powdered tablets containing 50 mg of dexamfetamine sulfate with 10 mL of *water*, filter, cool to about 15°, add 3 mL of 1M *sodium hydroxide* and shake for 2 minutes with 1 mL of a mixture of 1 volume of *benzoyl chloride* and 2 volumes of *ether*. Filter, wash the residue with 15 mL of *water* and recrystallise twice from *ethanol (50%)*. The *melting point* of the crystals, after drying at 105° for 1 hour, is about 156°, Appendix V A.

ASSAY

Weigh and powder 20 tablets, or more if necessary. Dissolve a quantity of the powder containing 0.1 g of Dexamfetamine Sulfate as completely as possible in 20 mL of *water*, add 8 g of *sodium chloride* and 2 mL of 5M *sodium hydroxide* and extract with successive quantities of 50, 20, 20 and 20 mL of *ether*. Extract the combined ether extracts with four 10 mL quantities of 0.1M *hydrochloric acid* and make the combined acid extracts alkaline with 5M *sodium hydroxide*. Dilute to 120 mL with *water* and distil into 20 mL of *0.05M hydrochloric acid VS* until only 5 mL of liquid remains in the distillation flask. Boil, cool and titrate the excess of acid with *0.05M sodium hydroxide VS* using *methyl red solution* as indicator. Each mL of *0.05M hydrochloric acid VS* is equivalent to 9.212 mg of $(C_9H_{13}N)_2,H_2SO_4$.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

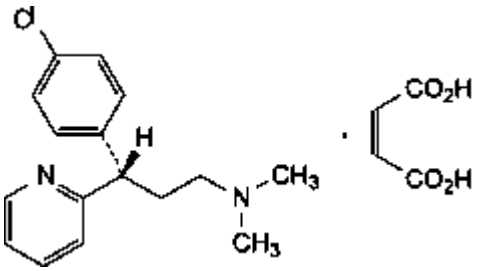
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dexchlorpheniramine Maleate

General Notices

(Ph. Eur. monograph 1196)



$C_{20}H_{23}ClN_2O_4$ 390.9 *2438-32-6*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

(3*S*)-3-(4-Chlorophenyl)-*N,N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (*Z*)-butenedioate.

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), in methanol and in methylene chloride.

IDENTIFICATION

First identification: A, C, E.

Second identification: A, B, D, E.

www.webofpharma.com

https://thuocngocanh.com/

A. Specific optical rotation (see Tests).

B. Melting point (2.2.14): 110 °C to 115 °C.

C. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs of *potassium bromide R*.

Comparison *dexchlorpheniramine maleate CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 56 mg of *maleic acid R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *anhydrous formic acid R*, *methanol R*, *di-isopropyl ether R* (3:7:20:70 *V/V/V/V*).

Application 5 µL.

Development Over a path of 12 cm.

Drying In a current of air for a few minutes.

Detection Examine in ultraviolet light at 254 nm.

Results The chromatogram obtained with the test solution shows 2 clearly separated spots. The upper spot is similar in position and size to the spot in the chromatogram obtained with the reference solution.

E. To 0.15 g in a porcelain crucible add 0.5 g of *anhydrous sodium carbonate R*. Heat over an open flame for 10 min. Allow to cool. Take up the residue with 10 mL of *dilute nitric acid R* and filter. To 1 mL of the filtrate add 1 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

pH (2.2.3)

4.5 to 5.5.

Dissolve 0.20 g in 20 mL of *water R*.

www.webofpharma.com

https://thuocngocanh.com/

Specific optical rotation (2.2.7)

+ 22 to + 23 (dried substance), determined on solution S.

Related substances

Gas chromatography (2.2.28).

Test solution Dissolve 10.0 mg of the substance to be examined in 1.0 mL of *methylene chloride R*.

Reference solution Dissolve 5.0 mg of *brompheniramine maleate CRS* in 0.5 mL of *methylene chloride R* and add 0.5 mL of the test solution. Dilute 0.5 mL of this solution to 50.0 mL with *methylene chloride R*.

Column:

— *material*: glass;

— *size*: *l* = 2.3 m, Ø = 2 mm;

— *stationary phase*: *silanised diatomaceous earth for gas chromatography R* (135-175 µm) impregnated with 3 per cent *m/m* of *phenyl(50)methyl(50)polysiloxane R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 20 mL/min.

Temperature:

— *column*: 205 °C;

— *injection port and detector*: 250 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time 2.5 times the retention time of dexchlorpheniramine.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to dexchlorpheniramine and brompheniramine.

Limits:

— *impurity A*: not more than 0.8 times the area of the peak due to dexchlorpheniramine in the chromatogram obtained with the reference solution (0.4 per cent);

— *total*: not more than twice the area of the peak due to dexchlorpheniramine in the chromatogram obtained with the reference solution (1 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 10.0 mg of the substance to be examined in 3 mL of water R. Add a few drops of concentrated ammonia R until an alkaline reaction is produced. Shake with 5 mL of methylene chloride R. Separate the layers. Evaporate the lower, methylene chloride layer to an oily residue on a water-bath. Dissolve the oily residue in 2-propanol R and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of dexchlorpheniramine maleate CRS in 3 mL of water R. Add a few drops of concentrated ammonia R until an alkaline reaction is produced. Shake with 5 mL of methylene chloride R. Separate the layers. Evaporate the lower, methylene chloride layer to an oily residue on a water-bath. Dissolve the oily residue in 2-propanol R and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of chlorphenamine maleate CRS in 3 mL of water R. Add a few drops of concentrated ammonia R until an alkaline reaction is produced. Shake with 5 mL of methylene chloride R. Separate the layers. Evaporate the lower, methylene chloride layer to an oily residue on a water-bath. Dissolve the oily residue in 2-propanol R and dilute to 10 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of the test solution to 50 mL with 2-propanol R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: amylose derivative of silica gel for chromatography R.

Mobile phase diethylamine R, 2-propanol R, hexane R (3:20:980 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Under these conditions the peak due to the (*S*)-isomer appears first.

System suitability:

— resolution: minimum 1.5 between the peaks due to the (*R*)-enantiomer (impurity B) and the (*S*)-enantiomer in the chromatogram obtained with reference solution (b);

— the retention times of the principal peaks in the chromatograms obtained with the test solution and reference solution (a) are identical ((*S*)-enantiomer).

Limits:

— *(R)-enantiomer* (impurity B): not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (2 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 65 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

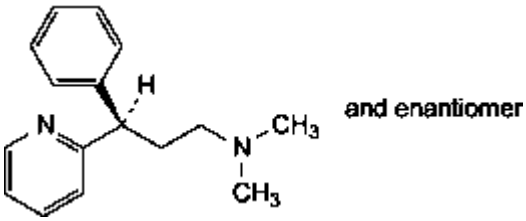
1 mL of *0.1 M perchloric acid* is equivalent to 19.54 mg of $C_{20}H_{23}ClN_2O_4$.

STORAGE

Protected from light.

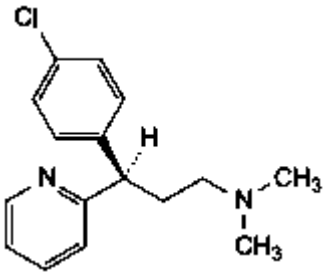
IMPURITIES

Specified impurities A, B.



and enantiomer

A. (3*RS*)-*N,N*-dimethyl-3-phenyl-3-(pyridin-2-yl)propan-1-amine,



B. (3*R*)-3-(4-chlorophenyl)-*N,N*-dimethyl-3-(pyridin-2-yl)propan-1-amine ((*R*)-enantiomer).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

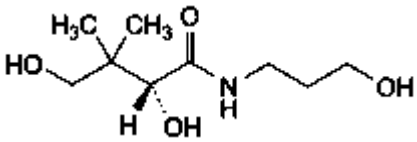
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Dexpanthenol

General Notices

(Ph. Eur. monograph 0761)



$C_9H_{19}NO_4$ 205.3 *81-13-0*

Action and use

Vitamin B_5 analogue.

Ph Eur

DEFINITION

(2*R*)-2,4-Dihydroxy-*N*-(3-hydroxypropyl)-3,3-dimethylbutanamide.

Content

98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Colourless or slightly yellowish, viscous, hygroscopic liquid, or a white or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent) and practically insoluble in heptane.

IDENTIFICATION

First identification: A, B.

Second identification: C.

www.webofpharma.com

https://thuocngocanh.com/

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs prepared as follows if recording in transmission mode: dissolve the substance to be examined and the reference substance separately in 1.0 mL of *anhydrous ethanol R* to obtain a concentration of 5 mg/mL. Place dropwise 0.5 mL of this solution on a disc of *potassium bromide R*. Dry the disc at 100-105 °C for 15 min.

Comparison *dexpanthenol CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of 0.25 mL of *water R* and 4 mL of *methanol R*.

Reference solution Dissolve 10 mg of *dexpanthenol CRS* in a mixture of 0.25 mL of *water R* and 4 mL of *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *2-propanol R* (5:15:80 *V/V/V*).

Application 5 µL.

Development Over 4/5 of the plate.

Drying In air.

Detection Heat at 120 °C for 20 min; treat the warm plate with a 3 g/L solution of *ninhydrin R* in a mixture of 3 volumes of *glacial acetic acid R* and 100 volumes of *anhydrous ethanol R*; allow to dry and heat again at 120 °C for a few minutes; examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_6 (2.2.2, *Method II*).

pH (2.2.3)

Maximum 10.5 for solution S.

Specific optical rotation (2.2.7)

+ 29.0 to + 32.0 (anhydrous substance), determined on solution S.

www.webofpharma.com

https://thuocngocanh.com/

Impurity A and other amino compounds

Maximum 1.0 per cent.

Dissolve 4.000 g in 60 mL of *glacial acetic acid R* and immediately titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 7.5 mg of C_3H_9NO.

Related substances

Liquid chromatography (*2.2.29*). *Protect the solutions from light*.

Buffer solution 1.78 g/L solution of *disodium hydrogen phosphate dihydrate R* adjusted to pH 7.0 with *phosphoric acid R*.

Test solution Dissolve 0.600 g of the substance to be examined in the buffer solution and dilute to 100.0 mL with the buffer solution.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the buffer solution. Dilute 1.0 mL of this solution to 10.0 mL with the buffer solution.

Reference solution (b) Dissolve 3 mg of *dexpanthenol impurity B CRS* and 3.0 mg of *pantolactone CRS* (impurity C) in the buffer solution and dilute to 100.0 mL with the buffer solution.

Reference solution (c) Dilute 1 mL of reference solution (b) to 10 mL with the buffer solution.

Reference solution (d) Dilute 1 mL of the test solution to 10 mL with reference solution (b).

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 1 volume of *acetonitrile R1* and 99 volumes of a 1.56 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 2.5 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	100	0
6 - 21	100 → 50	0 → 50

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
21 - 30	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to dexpanthenol (retention time = about 6 min): impurity B = about 0.4; impurity C = about 0.6.

System suitability:

— *resolution*: minimum 2.5 between the peaks due to impurities B and C and minimum 1.5 between the peaks due to impurity C and dexpanthenol in the chromatogram obtained with reference solution (d);

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity C in the chromatogram obtained with reference solution (c).

Calculation of percentage contents:

— for impurities B and C, use the concentration of impurity C in reference solution (b);

— for impurities other than B and C, use the concentration of dexpanthenol in reference solution (a).

Limits:

— *impurity C*: maximum 1.0 per cent;

— *impurity B*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

To 0.250 g add 50.0 mL of *0.1 M perchloric acid*. Boil under a reflux condenser for 7 h, protected from humidity. Allow to cool and transfer quantitatively to a titration vessel using *glacial acetic acid R*. Add 50.0 mL of a 9.02 g/L solution of *anhydrous sodium acetate R* in *glacial acetic acid R* and titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 20.53 mg of $C_9H_{19}NO_4$.

STORAGE

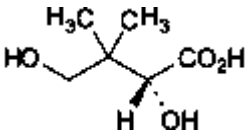
In an airtight container.

IMPURITIES

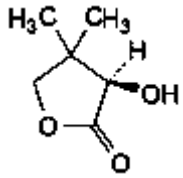
Specified impurities *A, B, C.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*

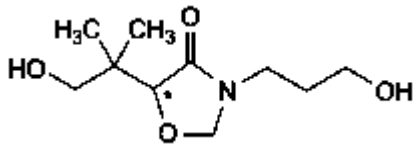
A. 3-aminopropan-1-ol,



B. (2*R*)-2,4-dihydroxy-3,3-dimethylbutanoic acid (pantoic acid),



C. (3*R*)-3-hydroxy-4,4-dimethyloxolan-2-one (pantolactone),



D. (5Ξ)-5-(1-hydroxy-2-methylpropan-2-yl)-3-(3-hydroxypropyl)-1,3-oxazolidin-4-one.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextran 1 for Injection

General Notices

(Ph. Eur. monograph 1506)

Action and use

Plasma substitute.

Ph Eur

DEFINITION

Low-molecular-weight fraction of dextran, consisting of a mixture of isomaltooligosaccharides.

Average relative molecular mass About 1000.

PRODUCTION

It is obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using *Leuconostoc mesenteroides* strain NRRL B-512 = CIP 78.59 or substrains thereof (for example *L. mesenteroides* B-512 F = NCTC 10817).

It is prepared in conditions designed to minimise the risk of microbial contamination.

CHARACTERS

Appearance

White or almost white hygroscopic powder.

Solubility

Very soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 3.000 g in *water R*, heat on a water-bath and dilute to 100.0 mL with the same solvent. The specific optical rotation (2.2.7) is + 148 to + 164, calculated with reference to the dried substance. Dry an aliquot of the solution first on a water-bath and then to constant weight *in vacuo* at 70 °C. Calculate the dextran content after correction for the content of sodium chloride.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation To 1-2 mg add 1 or a few drops of *water R*. Grind in an agate mortar for 1-2 min. Add about 300 mg of *potassium bromide R* and mix to a slurry but do not grind. Dry *in vacuo* at 40 °C for 15 min. Crush the residue. If it is not dry, dry for another 15 min. Prepare a

www.webofpharma.com

https://thuocngocanh.com/

disc with the residue.

Comparison Repeat the operations using *dextran 1 CRS*.

C. Molecular-mass distribution (see Tests).

TESTS

Solution S

Dissolve 7.5 g in *carbon dioxide-free water R*, heat on a water-bath and dilute to 50 mL with the same solvent.

Absorbance (*2.2.25*)

Maximum 0.12, determined at 375 nm on solution S.

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Add 0.2 mL of *0.01 M sodium hydroxide*. The solution is pink. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is colourless. Add 0.1 mL of *methyl red solution R*. The solution is red or orange.

Nitrogen-containing substances

Maximum 110 ppm of N.

Carry out the determination of nitrogen by sulfuric acid digestion (*2.5.9*), using 0.200 g and heating for 2 h. Collect the distillate in a mixture of 0.5 mL of *bromocresol green solution R*, 0.5 mL of *methyl red solution R* and 20 mL of *water R*. Titrate with *0.01 M hydrochloric acid*. Not more than 0.15 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Sodium chloride

Maximum 1.5 per cent.

Accurately weigh 3-5 g and dissolve in 100 mL of *water R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

Molecular-mass distribution

Size-exclusion chromatography (*2.2.30*).

Test solution Dissolve 6.0-6.5 mg of the substance to be examined in 1.0 mL of the mobile phase.

Reference solution (a) Dissolve 6.0-6.5 mg of *dextran 1 CRS* in 1.0 mL of the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *isomaltooligosaccharide CRS* in 1 mL of the mobile phase, and mix. This corresponds to approximately 45 µg of isomaltotriose (3 glucose units), approximately 45 µg of isomaltononaose (9 glucose units), and

www.webofpharma.com

https://thuocngocanh.com/

approximately 60 µg of sodium chloride per 100 µL.

Column 2 columns coupled in series:

— *size*: *l* = 0.30 m, Ø = 10 mm;

— *stationary phase*: dextran covalently bound to highly cross-linked porous agarose beads, allowing resolution of oligosaccharides in the molecular mass range of 180 to 3000;

— *temperature*: 20-25 °C.

Mobile phase 2.92 g/L solution of *sodium chloride R*.

Flow rate 0.07-0.08 mL/min maintained constant to ± 1 per cent.

Detection Differential refractometer.

Injection 100 µL.

Identification of peaks Use the chromatogram obtained with reference solution (b) to identify the peaks due to isomaltotriose, isomaltononaose and sodium chloride.

Determine the peak areas. Disregard any peak due to sodium chloride. Calculate the average relative molecular mass M_w and the amount of the fraction with less than 3 and more than 9 glucose units, of *dextran 1 CRS* and of the substance to be examined, using the following expression:

$$M_w = \sum w_i \times m_i$$

M_w = average molecular mass of the dextran;

m_i = molecular mass of oligosaccharide *i*;

w_i = weight proportion of oligosaccharide *i*.

Use the following m_i values for the calculation:

Oligosaccharide *i*	***m*$_i$**
glucose	180
isomaltose	342
isomaltotriose	504
isomaltotetraose	666
isomaltopentaose	828
isomaltohexaose	990

www.webofpharma.com

https://thuocngocanh.com/

Oligosaccharide *i*	m_i
isomaltoheptaose	1152
isomaltooctaose	1314
isomaltononaose	1476
isomaltodecaose	1638
isomaltoundecaose	1800
isomaltododecaose	1962
isomaltotridecaose	2124
isomaltotetradecaose	2286
isomaltopentadecaose	2448
isomaltohexadecaose	2610
isomaltoheptadecaose	2772
isomaltooctadecaose	2934
isomaltononadecaose	3096

System suitability The values obtained for *dextran 1 CRS* are within the values stated on the label.

Limits:

— *average molecular mass (M_w)*: 850 to 1150;

— *fraction with less than 3 glucose units*: less than 15 per cent;

— *fraction with more than 9 glucose units*: less than 20 per cent.

Loss on drying (*2.2.32*)

Maximum 5.0 per cent, determined on 5.000 g by drying in an oven at 105 °C for 5 h.

Bacterial endotoxins (*2.6.14*)

Less than 25 IU/g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextran 40 for Injection

General Notices

(Ph. Eur. monograph 0999)

Action and use

Plasma substitute.

Preparation

Dextran 40 Infusion

Ph Eur

DEFINITION

Mixture of polysaccharides, principally of the α-1,6-glucan type.

Average relative molecular mass About 40 000.

PRODUCTION

It is obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using *Leuconostoc mesenteroides* strain NRRL B-512 = CIP 78.59 or substrains thereof (for example *L. mesenteroides* B-512F = NCTC 10817).

It is prepared in conditions designed to minimise the risk of microbial contamination.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (2.2.7): + 195 to + 201 (dried substance).

Dissolve 1.0 g in *water R*, heating on a water-bath, and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *dextran CRS*.

C. Molecular-mass distribution (see Tests).

TESTS

Solution S

Dissolve 5.0 g in *distilled water R*, heating on a water-bath, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R*. The solution remains colourless. Add 0.2 mL of *0.01 M sodium hydroxide*. The solution is red. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is colourless. Add 0.1 mL of *methyl red solution R*. The solution is red or orange.

Nitrogen-containing substances

Maximum 110 ppm N.

Carry out the determination of nitrogen by sulfuric acid digestion (*2.5.9*), using 0.200 g and heating for 2 h. Collect the distillate in a mixture of 0.5 mL of *bromocresol green solution R*, 0.5 mL of *methyl red solution R* and 20 mL of *water R*. Titrate with *0.01 M hydrochloric acid*. Not more than 0.15 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Residual solvents

Gas chromatography (*2.2.28*).

Internal standard *propanol R*.

Test solution Dissolve 5 g of the substance to be examined in 100 mL of *water R* and distil. Collect the first 45 mL of the distillate, add 1 mL of a 25 g/L solution of *propanol R* and dilute to 50 mL with *water R*.

Reference solution Mix 0.5 mL of a 25 g/L solution of *anhydrous ethanol R*, 0.5 mL of a 25 g/L solution of *propanol R* and 0.5 mL of a 2.5 g/L solution of *methanol R* and dilute to 25.0 mL with *water R*.

Column:

— *material*: stainless steel;

— *size*: *l* = 1.8 m, Ø = 2 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (125-150 µm).

Carrier gas *nitrogen for chromatography R*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Flow rate 25 mL/min.

Temperature:

— *column*: 190 °C;

— *injection port*: 240 °C;

— *detector*: 210 °C.

Detection Flame ionisation.

Injection The chosen volume of each solution.

Limits:

— *ethanol*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.5 per cent);

— *methanol*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.05 per cent);

— *sum of solvents other than ethanol, methanol and propanol*: not more than the area of the peak due to the internal standard (0.5 per cent, calculated as propanol).

Molecular-mass distribution (*2.2.39*)

The average molecular mass (M_w) is 35 000 to 45 000. The average molecular mass of the 10 per cent high fraction is not greater than 110 000. The average molecular mass of the 10 per cent low fraction is not less than 7000.

Loss on drying (*2.2.32*)

Maximum 7.0 per cent, determined on 0.200 g by heating in an oven at 105 ± 2 °C for 5 h.

Sulfated ash (*2.4.14*)

Maximum 0.3 per cent, determined on 0.50 g.

Bacterial endotoxins (*2.6.14*)

Less than 10 IU/g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextran 40 Infusion

General Notices

Dextran 40 Injection, Dextran 40 Intravenous Infusion

Action and use

Plasma substitute.

DEFINITION

Dextran 40 Infusion is a sterile solution containing Dextran 40 for Injection in Glucose Infusion or in Sodium Chloride Infusion. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of dextrans

9.0 to 11.0% w/v.

CHARACTERISTICS

An almost colourless, slightly viscous solution.

TESTS

Acidity

Titrate 25 mL with *0.01M sodium hydroxide VS* using *phenol red solution* as indicator. Not more than 2.0 mL of *0.01M sodium hydroxide VS* is required to neutralise the solution.

Molecular size

For solutions in Glucose Infusion, before proceeding with tests A, B and C add 4 volumes of *ethanol (96%)*, centrifuge and dissolve the residue in sufficient Sodium Chloride Infusion to restore the original volume.

A. Determine the viscosities, Appendix V H, Method I, at 37°, using a U-tube viscometer (size C) of solutions in *saline solution* containing about 3.5, 2.5, 1.5 and 0.75% w/v of Dextrans, accurately determined. Calculate the viscosity ratio by dividing the time taken for the meniscus to fall from E to F using the liquid being examined by the time taken using *saline solution*. For each solution plot (viscosity ratio – 1.00)/concentration against concentration. The intercept on the viscosity ratio axis of a straight line through the points represents the intrinsic viscosity. The intrinsic viscosity is 0.16 to 0.20.

B. Dilute the solution being examined with *saline solution* to contain 6% w/v of Dextrans. Place 100 mL in each of five stoppered flasks and adjust the temperature to 24.9° to 25.1°. Maintaining this temperature, add slowly with continuous stirring sufficient *absolute ethanol* to

www.webofpharma.com

https://thuocngocanh.com/

produce a faint cloudiness (about 45 mL). To the separate flasks add 0.5, 1.0, 1.5, 2.0 and 2.5 mL of *absolute ethanol*, stopper the flasks and immerse in a water bath at about 35°, shaking occasionally, until clear solutions are obtained. Transfer the flasks to a water bath maintained at 24.9° to 25.1° and allow to stand overnight or until two clear liquid phases are formed. Discard the supernatant liquids, dissolve separately the syrupy residues in sufficient *saline solution* to produce 25.0 mL, remove the ethanol by evaporation at a pressure of 2 kPa, dilute to 25.0 mL with *water* and determine the *optical rotation*, Appendix V F. From the optical rotations calculate the amounts of dextrans precipitated as described in the Assay. Choose that fraction containing as nearly as possible but not more than 10% of the dextrans present in the infusion and determine its intrinsic viscosity by the method described under test A using a U-tube viscometer (size A). The intrinsic viscosity is not more than 0.27.

C. Place in each of four stoppered flasks 100 mL of the diluted infusion in *saline solution* containing 6% w/v of Dextrans and add slowly, with continuous stirring, 80, 90, 100 and 110 mL respectively of *absolute ethanol*. Stopper the flasks, transfer to a water bath maintained at 24.9° to 25.1° and allow to stand overnight or until two clear liquid phases are formed. Separate the supernatant solutions from the syrupy residues. Remove the ethanol from each supernatant solution separately by evaporation at a pressure of 2 kPa, dialyse in cellophane tubing against *water* to remove sodium chloride, adjust the volume to 25.0 mL with *water*, add sufficient *sodium chloride* to produce solutions containing 0.9% w/v and determine the *optical rotation*, Appendix V F. From the optical rotations calculate the amounts of dextrans present as described in the Assay. Choose that fraction containing as nearly as possible but not more than 10% of the dextrans present in the infusion and determine the intrinsic viscosity by the method in test A above. The intrinsic viscosity is not less than 0.08.

Content of glucose

For solutions in Glucose Infusion, 4.5 to 5.5% w/v, when determined by the following method. Dilute 15 mL to 50 mL with *water*. To 5 mL in a stoppered flask add 25 mL of a buffer solution containing 14.3% w/v of *sodium carbonate* and 4.0% w/v of *potassium iodide* and 25 mL of *0.05M iodine VS*. Stopper the flask, allow to stand for exactly 30 minutes at 20°, add 35 mL of *2M hydrochloric acid* and titrate immediately with 0.1M *sodium thiosulfate VS*. Repeat the operation using 5 mL of *water* beginning at the words ‘add 25 mL...’. The difference between the titrations represents the amount of iodine required to oxidise the glucose. Each mL of *0.05M iodine VS* is equivalent to 9.01 mg of glucose.

Bacterial endotoxins

The endotoxin limit concentration is 1.25 IU per mL, Appendix XIV C.

ASSAY

For solutions in Glucose Infusion

Add 0.05 mL of 5M *ammonia* to the required volume and measure the *optical rotation*, Appendix V F. Calculate the content of dextrans from the expression

$$0.5076(\alpha - 0.528D)$$

where α is the observed angular rotation and *D* is the content of glucose as a percentage w/v determined in the test for Content of glucose.

For solutions in Sodium Chloride Infusion

Measure the *optical rotation*, Appendix V F, and multiply the value obtained by 0.5076.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

Dextran 40 Infusion should not be exposed to undue fluctuations of temperature.

LABELLING

The strength is stated as the percentage w/v of dextrans. The label states (1) the name of the solvent; (2) that the infusion should not be used if it is cloudy or if a deposit is present.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextran 60 for Injection

General Notices

(Ph. Eur. monograph 1000)

Action and use

Plasma substitute.

Ph Eur

DEFINITION

Mixture of polysaccharides, principally of the α-1,6-glucan type.

Average relative molecular mass About 60 000.

PRODUCTION

It is obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using *Leuconostoc mesenteroides* strain NRRL B-512 = CIP 78.59 or substrains thereof (for example *L. mesenteroides* B-512F = NCTC 10817).

It is prepared in conditions designed to minimise the risk of microbial contamination.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (2.2.7): + 195 to + 201 (dried substance).

Dissolve 1.0 g in *water R*, heating on a water-bath, and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dextran CRS*.

C. Molecular-mass distribution (see Tests).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 5.0 g in *distilled water R*, heating on a water-bath, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R*. The solution remains colourless. Add 0.2 mL of *0.01 M sodium hydroxide*. The solution is red. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is colourless. Add 0.1 mL of *methyl red solution R*. The solution is red or orange.

Nitrogen-containing substances

Maximum 110 ppm of N.

Carry out the determination of nitrogen by sulfuric acid digestion (*2.5.9*), using 0.200 g and heating for 2 h. Collect the distillate in a mixture of 0.5 mL of *bromocresol green solution R*, 0.5 mL of *methyl red solution R* and 20 mL of *water R*. Titrate with *0.01 M hydrochloric acid*. Not more than 0.15 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Residual solvents

Gas chromatography (*2.2.28*).

Internal standard *propanol R*.

Test solution Dissolve 5 g of the substance to be examined in 100 mL of *water R* and distil. Collect the first 45 mL of the distillate, add 1 mL of a 25 g/L solution of *propanol R* and dilute to 50 mL with *water R*.

Reference solution Mix 0.5 mL of a 25 g/L solution of *anhydrous ethanol R*, 0.5 mL of a 25 g/L solution of *propanol R* and 0.5 mL of a 2.5 g/L solution of *methanol R* and dilute to 25.0 mL with *water R*.

Column:

— *material*: stainless steel;

— *size*: *l* = 1.8 m, Ø = 2 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (125-150 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 25 mL/min.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

— *column*: 190 °C;

— *injection port*: 240 °C;

— *detector*: 210 °C.

Detection Flame ionisation.

Injection The chosen volume of each solution.

Limits:

— *ethanol*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.5 per cent);

— *methanol*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.05 per cent);

— *sum of solvents other than ethanol, methanol and propanol*: not more than the area of the peak due to the internal standard (0.5 per cent, calculated as propanol).

Molecular-mass distribution (2.2.39)

The average molecular mass (M_w) is 54 000 to 66 000. The average molecular mass of the 10 per cent high fraction is not greater than 180 000. The average molecular mass of the 10 per cent low fraction is not less than 14 000.

Loss on drying (2.2.32)

Maximum 7.0 per cent, determined on 0.200 g by heating in an oven at 105 ± 2 °C for 5 h.

Sulfated ash (2.4.14)

Maximum 0.3 per cent, determined on 0.50 g.

Bacterial endotoxins (2.6.14)

Less than 16 IU/g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextran 70 for Injection

General Notices

(Ph. Eur. monograph 1001)

Action and use

Plasma substitute.

Preparation

Dextran 70 Infusion

Ph Eur

DEFINITION

Mixture of polysaccharides, principally of the α-1,6-glucan type.

Average relative molecular mass About 70 000.

PRODUCTION

It is obtained by hydrolysis and fractionation of dextrans produced by fermentation of sucrose using *Leuconostoc mesenteroides* strain NRRL B-512 = CIP 78.59 or substrains thereof (for example *L. mesenteroides* B-512F = NCTC 10817).

It is prepared in conditions designed to minimise the risk of microbial contamination.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (2.2.7): + 195 to + 201 (dried substance).

Dissolve 1.0 g in *water R*, heating on a water-bath, and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *dextran CRS*.

C. Molecular-mass distribution (see Tests).

TESTS

Solution S

Dissolve 5.0 g in *distilled water R*, heating on a water-bath, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *phenolphthalein solution R*. The solution remains colourless. Add 0.2 mL of *0.01 M sodium hydroxide*. The solution is red. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is colourless. Add 0.1 mL of *methyl red solution R*. The solution is red or orange.

Nitrogen-containing substances

Maximum 110 ppm of N.

Carry out the determination of nitrogen by sulfuric acid digestion (*2.5.9*), using 0.200 g and heating for 2 h. Collect the distillate in a mixture of 0.5 mL of *bromocresol green solution R*, 0.5 mL of *methyl red solution R* and 20 mL of *water R*. Titrate with *0.01 M hydrochloric acid*. Not more than 0.15 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Residual solvents

Gas chromatography (*2.2.28*).

Internal standard *propanol R*.

Test solution Dissolve 5 g of the substance to be examined in 100 mL of *water R* and distil. Collect the first 45 mL of the distillate, add 1 mL of a 25 g/L solution of *propanol R* and dilute to 50 mL with *water R*.

Reference solution Mix 0.5 mL of a 25 g/L solution of *anhydrous ethanol R*, 0.5 mL of a 25 g/L solution of *propanol R* and 0.5 mL of a 2.5 g/L solution of *methanol R* and dilute to 25.0 mL with *water R*.

Column:

— *material*: stainless steel;

— *size*: *l* = 1.8 m, Ø = 2 mm;

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (125-150 µm).

Carrier gas *nitrogen for chromatography R*.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 25 mL/min.

Temperature:

— *column*: 190 °C;

— *injection port*: 240 °C;

— *detector*: 210 °C.

Detection Flame ionisation.

Injection The chosen volume of each solution.

Limits:

— *ethanol*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.5 per cent);

— *methanol*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.05 per cent);

— *sum of solvents other than ethanol, methanol and propanol*: not more than the area of the peak due to the internal standard (0.5 per cent, calculated as propanol).

Molecular-mass distribution (*2.2.39*)

The average molecular mass (M_w) is 64 000 to 76 000. The average molecular mass of the 10 per cent high fraction is not greater than 185 000. The average molecular mass of the 10 per cent low fraction is not less than 15 000.

Loss on drying (*2.2.32*)

Maximum 7.0 per cent, determined on 0.200 g by heating in an oven at 105 ± 2 °C for 5 h.

Sulfated ash (*2.4.14*)

Maximum 0.3 per cent, determined on 0.50 g.

Bacterial endotoxins (*2.6.14*)

Less than 16 IU/g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextran 70 Infusion

General Notices

Dextran 70 Injection, Dextran 70 Intravenous Infusion

Action and use

Plasma substitute.

DEFINITION

Dextran 70 Infusion is a sterile solution containing Dextran 70 for Injection, in Glucose Infusion or in Sodium Chloride Infusion. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of dextrans

5.5 to 6.5% w/v.

CHARACTERISTICS

An almost colourless, slightly viscous solution.

TESTS

Acidity

Titrate 25 mL with *0.01M sodium hydroxide VS* using *phenol red solution* as indicator. Not more than 1.25 mL of *0.01M sodium hydroxide VS* is required to neutralise the solution.

Molecular size

For solutions in Glucose Infusion, before proceeding with tests A, B and C add 4 volumes of *ethanol (96%)*, centrifuge and dissolve the residue in sufficient Sodium Chloride Infusion to restore the original volume.

A. Determine the viscosities, Appendix V H, Method I, at 37°, using a U-tube viscometer (size C) of solutions in *saline solution* containing about 3.5, 2.5, 1.5 and 0.75% w/v of Dextrans, accurately determined. Calculate the viscosity ratio by dividing the time taken for the meniscus to fall from E to F using the liquid being examined by the time taken using *saline solution*. For each solution plot (viscosity ratio – 1.00)/concentration against concentration. The intercept on the viscosity ratio axis of a straight line through the points represents the intrinsic viscosity. The intrinsic viscosity is 0.22 to 0.27.

B. Place 100 mL in each of five stoppered flasks and adjust the temperature to 24.9° to 25.1°. Maintaining this temperature, add slowly with continuous stirring sufficient *absolute ethanol* to produce a faint cloudiness (about 45 mL). To the separate flasks add 0.5, 1.0, 1.5, 2.0

www.webofpharma.com

https://thuocngocanh.com/

and 2.5 mL of *absolute ethanol*, stopper the flasks and immerse in a water bath at about 35°, shaking occasionally, until clear solutions are obtained. Transfer the flasks to a water bath maintained at 24.9° to 25.1° and allow to stand overnight or until two clear liquid phases are formed. Discard the supernatant liquids, dissolve separately the syrupy residues in sufficient *saline solution* to produce 25.0 mL, remove the ethanol by evaporation at a pressure of 2 kPa, dilute to 25.0 mL with *water* and determine the *optical rotation*, Appendix V F. From the optical rotations calculate the amounts of dextrans precipitated as described in the Assay. Choose that fraction containing as nearly as possible but not more than 10% of the dextrans present in the infusion and determine its intrinsic viscosity by the method described under test A using a U-tube viscometer (size A). The intrinsic viscosity is not more than 0.36.

C. Dilute the solution being examined with *saline solution* to contain 6% w/v of Dextrans. Place 100 mL in each of four stoppered flasks and add slowly, with continuous stirring, 80, 90, 100 and 110 mL respectively of *absolute ethanol*. Stopper the flasks, transfer to a water bath maintained at 24.9° to 25.1° and allow to stand overnight or until two clear liquid phases are formed. Separate the supernatant solutions from the syrupy residues. Remove the ethanol from each supernatant solution separately by evaporation at a pressure of 2 kPa, dialyse in cellophane tubing against *water* to remove sodium chloride, adjust the volume to 25.0 mL with *water*, add sufficient *sodium chloride* to produce solutions containing 0.9% w/v and determine the *optical rotation*, Appendix V F. From the optical rotations calculate the amounts of dextrans present as described in the Assay. Choose that fraction containing as nearly as possible but not more than 10% of the dextrans present in the infusion and determine the intrinsic viscosity by the method in test A. The intrinsic viscosity is not less than 0.13.

Content of glucose

For solutions in Glucose Infusion, 4.5 to 5.5% w/v, when determined by the following method. Dilute 15 mL to 50 mL with *water*. To 5 mL in a stoppered flask add 25 mL of a buffer solution containing 14.3% w/v of *sodium carbonate* and 4.0% w/v of *potassium iodide* and 25 mL of *0.05M iodine VS*. Stopper the flask, allow to stand for exactly 30 minutes at 20°, add 35 mL of *2M hydrochloric acid* and titrate immediately with 0.1M *sodium thiosulfate VS*. Repeat the operation using 5 mL of *water* and beginning at the words ‘add 25 mL...’. The difference between the titrations represents the amount of iodine required to oxidise the glucose. Each mL of *0.05M iodine VS* is equivalent to 9.01 mg of glucose.

Bacterial endotoxins

The endotoxin limit concentration is 1.21 IU per mL, Appendix XIV C.

ASSAY

For solutions in Glucose Infusion

Add 0.05 mL of 5M *ammonia* to the required volume and measure the *optical rotation*, Appendix V F. Calculate the content of dextrans from the expression

$$0.5076(\alpha - 0.528D)$$

where α is the observed angular rotation and *D* is the content of glucose as a percentage w/v determined in the test for Content of glucose.

For solutions in Sodium Chloride Infusion

Measure the *optical rotation*, Appendix V F, and multiply the value obtained by 0.5076.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

Dextran 70 Infusion should not be exposed to undue fluctuations in temperature.

LABELLING

The strength is stated as the percentage w/v of dextrans. The label states (1) the name of the solvent; (2) that the infusion should not be used if it is cloudy or if a deposit is present.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextranomer

General Notices

(Ph. Eur. monograph 2238)

56087-11-7

Action and use

Fluid absorber; treatment of burns, wounds and skin ulcers; preparation for skin grafting.

Ph Eur

DEFINITION

Three-dimensional network made of dextran chains *O*,*O*′-cross-linked with 2-hydroxypropane-1,3-diyl bridges and *O*-substituted with 2,3-dihydroxypropyl and 2-hydroxy-1-(hydroxymethyl)ethyl groups.

CHARACTERS

Appearance

White or almost white, spherical beads.

Solubility

Practically insoluble in water. It swells in water and in electrolyte solutions.

PRODUCTION

The absorption capacity is determined using a 9.0 g/L solution of *sodium chloride R* containing 20 µL/L of *polysorbate 20 R* or another suitable solution, with a suitable, validated method.

The particle size is controlled to a minimum of 80 per cent of the number of dry beads within 100-300 µm and a maximum of 7 per cent of their number below 100 µm using a suitable, validated method.

IDENTIFICATION

A. The substance to be examined is practically insoluble in *water R*. It swells in *water R*.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Grind the substance to be examined in *acetone R*. Evaporate the solvent at room temperature and use the residue.

Comparison *dextranomer CRS*.

www.webofpharma.com

https://thietbiuocngocanh.com/

TESTS

pH (2.2.3)

5.3 to 7.5.

Introduce 0.50 g to 30 mL of a freshly prepared 74.6 g/L solution of *potassium chloride R*. Allow to stand for 2 min. Determine the pH on the mucilage obtained.

Boron

Maximum 30 ppm.

Inductively coupled plasma-atomic emission spectrometry (ICP-AES) (2.2.57).

Test solution Introduce 3.0 g into a platinum dish and moisten with 5 mL of a 32.1 g/L solution of *magnesium nitrate R* in a mixture of equal volumes of *ethanol (96 per cent) R* and *distilled water R*. Evaporate to dryness on a water-bath. Ignite at 550 °C for 5 h. Take up the residue with 5 mL of *6 M hydrochloric acid R* and transfer to a 50 mL volumetric flask. Add about 20 mL of *distilled water R* and allow to digest for 1 h on a water-bath. Allow to cool and dilute to 50.0 mL with *distilled water R*.

Reference solutions Prepare the reference solutions using a solution of *boric acid R* containing 10 ppm of boron. Proceed as described for the test solution.

Wavelength 249.773 nm.

Loss on drying (2.2.32)

Maximum 10.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 15 h.

Sulfated ash (2.4.14)

Maximum 0.4 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (2.6.12), determined using the pour-plate method.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextrin

General Notices

(Ph. Eur. monograph 1507)

9004-53-9

Action and use

Excipient.

Ph Eur

DEFINITION

Maize, potato or cassava starch partly hydrolysed and modified by heating with or without the presence of acids, alkalis or pH-control agents.

CHARACTERS

Appearance

White or almost white, free-flowing powder.

Solubility

Very soluble in boiling water forming a mucilaginous solution, slowly soluble in cold water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Suspend 1 g in 50 mL of *water R*, boil for 1 min and cool. To 1 mL of the solution add 0.05 mL of *iodine solution R1*. A dark blue or reddish-brown colour is produced, which disappears on heating.

B. Centrifuge 5 mL of the mucilage obtained in identification test A. To the upper layer add 2 mL of *dilute sodium hydroxide solution R* and, dropwise with shaking, 0.5 mL of *copper sulfate solution R* and boil. A red precipitate is produced.

C. It is very soluble in boiling *water R*, forming a mucilaginous solution.

TESTS

pH (*2.2.3*)

2.0 to 8.0.

Disperse 5.0 g in 100 mL of *carbon dioxide-free water R*.

www.webofpharma.com

https://thietbiuocngocanh.com/

Chlorides

Maximum 0.2 per cent.

Dissolve 2.5 g in 50 mL of boiling *water R*, dilute to 100 mL with *water R* and filter. Dilute 1 mL of the filtrate to 15 mL with *water R* and add 1 mL of *dilute nitric acid R*. Pour the mixture as a single addition into 1 mL of *silver nitrate solution R2* and allow to stand for 5 min protected from light. When viewed transversely against a black background any opalescence produced is not more intense than that obtained by treating a mixture of 10 mL of *chloride standard solution (5 ppm Cl) R* and 5 mL of *water R*, prepared in the same manner.

Reducing sugars

Maximum 10 per cent, calculated as glucose $C_6H_{12}O_6$.

To a quantity of dextrin equivalent to 2.0 g (dried substance) add 100 mL of *water R*, shake for 30 min, dilute to 200.0 mL with *water R* and filter. To 10.0 mL of alkaline *cupri-tartaric solution R* add 20.0 mL of the filtrate, mix, and heat on a hot plate adjusted to bring the solution to boil within 3 min. Boil for 2 min, and cool immediately. Add 5 mL of a 300 g/L solution of *potassium iodide R* and 10 mL of *dilute sulfuric acid R*, mix, and titrate immediately with *0.1 M sodium thiosulfate*, using *starch solution R*, added towards the end of the titration, as indicator. Repeat the procedure beginning with “To 10.0 mL of...”, using, in place of the filtrate, 20.0 mL of a 1 g/L solution of *glucose R*, accurately prepared. Perform a blank titration. ($V_B - V_U$) is not greater than ($V_B - V_S$), in which V_B, V_U and V_S are the number of millilitres of *0.1 M sodium thiosulfate* consumed in the titrations of the blank, the dextrin and the glucose, respectively.

Loss on drying (*2.2.32*)

Maximum 13.0 per cent, determined on 1.000 g by drying at 130 ± 5 °C for 90 min.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for dextrin used as filler and binder, in tablets and capsules.

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*)

The following characteristic may be relevant for dextrin used as viscosity-increasing agent.

www.webofpharma.com

https://thietbiuocngocanh.com/

Apparent viscosity (*2.2.10*)

Typically 100 mPa·s to 350 mPa·s (dried substance), depending on the grade of dextrin.

In a beaker, prepare a 10-50 per cent slurry so that the viscosity value ranges from 100 mPa·s to 350 mPa·s. The total mass of the sample plus water must be 600 g. Mix with a plastic rod to obtain a homogeneous slurry. Place the beaker in a water-bath at 100 ± 1 °C. Introduce the paddle of a stirrer into the beaker and close the beaker with a lid. Start agitation at 250 r/min as rapidly as possible and carry on for exactly 30 min. Transfer the paste immediately to the beaker to be used for viscosity measurement, placed in a water-bath at 40 ± 1 °C. Stir until the temperature in the beaker is 40 ± 1 °C then measure the apparent viscosity using spindle no. 2 and a rotation speed of 100 r/min.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

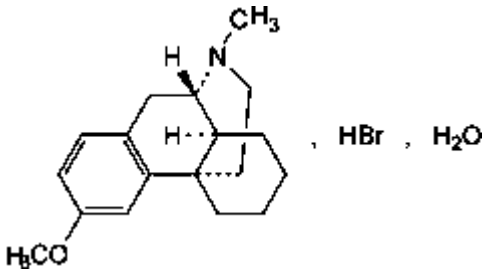
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextromethorphan Hydrobromide

General Notices

(Ph. Eur. monograph 0020)



$C_{18}H_{26}BrNO,H_2O$ 370.3 *6700-34-1*

Action and use

Opioid receptor agonist; cough suppressant.

Ph Eur

DEFINITION

ent-3-Methoxy-17-methylmorphinan hydrobromide monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent).

mp

About 125 °C, with decomposition.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, B, D.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dextromethorphan hydrobromide CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 25 mg of *dextromethorphan hydrobromide CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *methylene chloride R*, *methanol R*, *ethyl acetate R*, *toluene R* (2:10:13:20:55 *V/V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *potassium iodobismuthate solution R2*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of bromides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in *ethanol (96 per cent) R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

Dissolve 0.4 g in *carbon dioxide-free water R* with gentle heating, cool and dilute to 20 mL with the same solvent. Add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Specific optical rotation (2.2.7)

www.webofpharma.com

https://thuocngocanh.com/

+ 28 to + 30 (anhydrous substance).

Dissolve 0.200 g in *0.1 M hydrochloric acid* and dilute to 10.0 mL with the same acid.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *dextromethorphan impurity A CRS* in 2 mL of the test solution and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 3.11 g of *docusate sodium R* in a mixture of 400 mL of *water R* and 600 mL of *acetonitrile R*, add 0.56 g of *sodium nitrate R* and adjust to apparent pH 2.0 with *glacial acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time Twice the retention time of dextromethorphan.

Relative retention With reference to dextromethorphan (retention time = about 22 min): impurity B = about 0.4; impurity C = about 0.8; impurity D = about 0.9; impurity A = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to dextromethorphan and impurity A.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.2;

— *impurities A, B, C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), and not more than 1 such peak has an area greater than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

N,N-Dimethylaniline

Maximum 10 ppm.

Dissolve 0.5 g with heating in 20 mL of *water R*. Allow to cool, add 2 mL of *dilute acetic acid R* and 1 mL of a 10 g/L solution of *sodium nitrite R* and dilute to 25 mL with *water R*. The solution is not more intensely coloured than a reference solution prepared at the same time and in the same manner using 20 mL of a 0.25 mg/L solution of *N,N-dimethylaniline R*.

Water (*2.5.12*)

4.0 per cent to 5.5 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 20 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

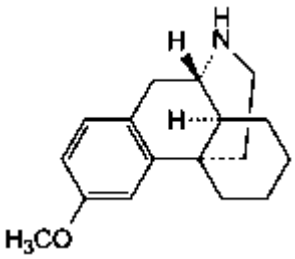
1 mL of *0.1 M sodium hydroxide* is equivalent to 35.23 mg of $C_{18}H_{26}BrNO$.

STORAGE

Protected from light.

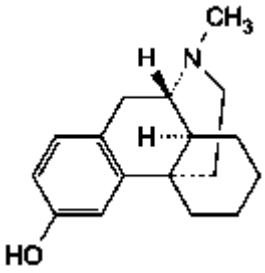
IMPURITIES

Specified impurities *A, B, C, D.*

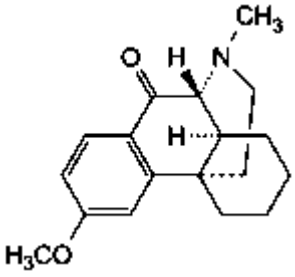


A. *ent*-3-methoxymorphinan,

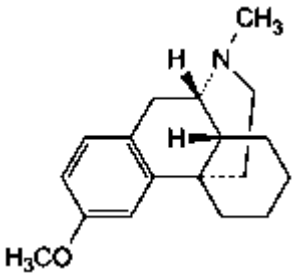
www.webofpharma.com



B. *ent*-17-methylmorphinan-3-ol,



C. *ent*-3-methoxy-17-methylmorphinan-10-one,



D. *ent*-(14*S*)-3-methoxy-17-methylmorphinan.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

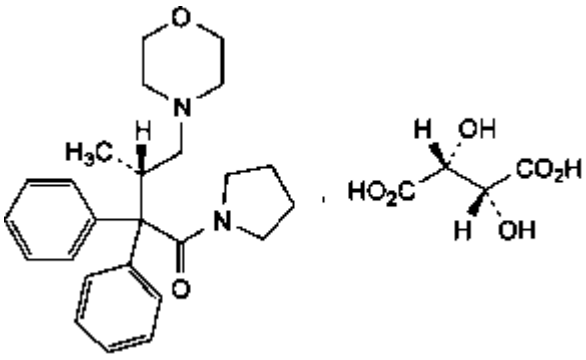
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Dextromoramide Tartrate

General Notices

(Ph. Eur. monograph 0021)



$C_{29}H_{38}N_2O_8$ 542.6 *2922-44-3*

Action and use

Opioid receptor agonist; analgesic.

Ph Eur

DEFINITION

Dextromoramide tartrate contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of 1-[(3*S*)-3-methyl-4-(morpholin-4-yl)-2,2-diphenylbutanoyl]pyrrolidine hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, amorphous or crystalline powder, soluble in water, sparingly soluble in ethanol (96 per cent).

It melts at about 190 °C, with slight decomposition.

IDENTIFICATION

A. Dissolve 75 mg in *1 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Examined between 230 nm and 350 nm (2.2.25), the solution shows 3 absorption maxima, at 254 nm, 259 nm and 264 nm. The specific absorbances at the maxima are about 6.9, 7.7 and 6.5, respectively.

www.webofpharma.com

https://thuocngocanh.com/

B. Dissolve about 50 mg in *water R* and dilute to 10 mL with the same solvent. To 2 mL of the solution add 3 mL of *ammoniacal silver nitrate solution R* and heat on a water-bath. A grey or black precipitate is formed.

C. It gives reaction (b) of tartrates (*2.3.1*).

TESTS

pH (*2.2.3*)

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent. The pH of the solution is 3.0 to 4.0.

Specific optical rotation (*2.2.7*)

Dissolve 0.50 g in *0.1 M hydrochloric acid* and dilute to 10.0 mL with the same acid. The specific optical rotation is + 21 to + 23.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution Dissolve 0.2 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dilute 1 mL of the test solution to 100 mL with *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using *methanol R*. Allow the plate to dry in air and spray with *dilute potassium iodobismuthate solution R*. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (1.0 per cent).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.00 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.05 M perchloric acid* using 0.15 mL of *naphtholbenzein solution R* as indicator.

1 mL of *0.05 M perchloric acid* is equivalent to 27.13 mg of $C_{29}H_{38}N_2O_8$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

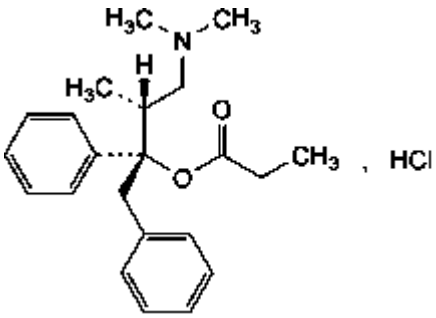
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dextropropoxyphene Hydrochloride

General Notices

(Ph. Eur. monograph 0713)



$C_{22}H_{30}ClNO_2$ 375.9 *1639-60-7*

Action and use

Opioid receptor agonist; analgesic.

Preparation

Co-proxamol Tablets

Ph Eur

DEFINITION

(1*S*,2*R*)-1-Benzyl-3-(dimethylamino)-2-methyl-1-phenylpropyl propanoate hydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

mp

www.webofpharma.com

https://thuocngocanh.com/

About 165 °C.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *dextropropoxyphene hydrochloride CRS*.

C. Solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.5 g in *carbon dioxide-free water R* and dilute to 30 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

Dilute 10 mL of solution S to 25 mL with *carbon dioxide-free water R*. To 10 mL of this solution add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Specific optical rotation (*2.2.7*)

+ 52 to + 57.

Dissolve 0.100 g in *water R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *methanol R* (50:50 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2 mg of *dextropropoxyphene for system suitability CRS* (containing impurities A, B, C and D) in 1.0 mL of the solvent mixture.

Reference solution (c) Dilute 1.0 mL of *toluene R* to 50.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 2.5 g of ammonium phosphate R in water R, adjust to pH 5.6 with dilute phosphoric acid R and dilute to 1000 mL with the same solvent;

— *mobile phase B*: acetonitrile R1.

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	85	15
2 - 7	85 → 75	15 → 25
7 - 24	75 → 50	25 → 50
24 - 32	50 → 40	50 → 60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with dextropropoxyphene for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and D. Use the chromatogram obtained with reference solution (c) to identify the peak due to toluene.

Relative retention With reference to dextropropoxyphene (retention time = about 18 min): impurity A = about 0.8; impurity B = about 0.9; impurity D = about 1.1; impurity C = about 1.2.

System suitability Reference solution (b):

— peak-to-valley ratio: minimum 5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to dextropropoxyphene.

Limits:

— *impurities A, B*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities C, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to toluene (relative retention = about 1.24).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.270 g in 60 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 37.59 mg of $C_{22}H_{30}ClNO_2$.

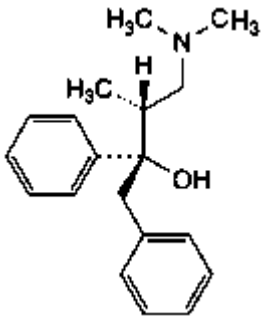
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D.*

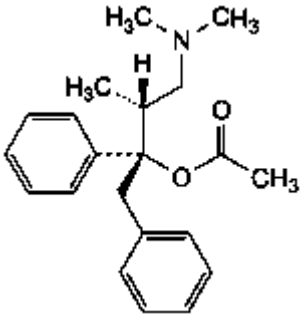
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F.*



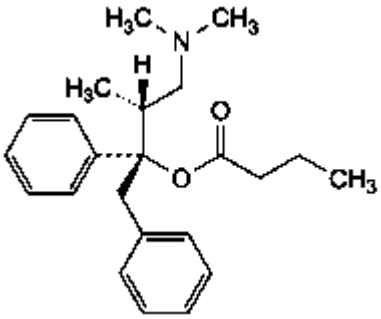
A. (2*S*,3*R*)-4-(dimethylamino)-1,2-diphenyl-3-methyl-butan-2-ol (oxyphene),

www.webofpharma.com

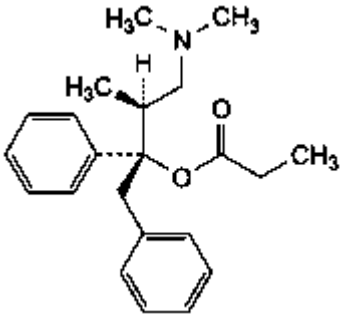
https://thuvienthuocngocanh.com/



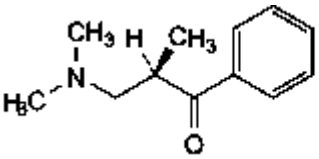
B. (1*S*,2*R*)-1-benzyl-3-(dimethylamino)-2-methyl-1-phenylpropyl acetate (acetoxyphene),



C. (1*S*,2*R*)-1-benzyl-3-(dimethylamino)-2-methyl-1-phenylpropyl butanoate (butyroxyphene),



D. (1*S*,2*S*)-1-benzyl-3-(dimethylamino)-2-methyl-1-phenylpropyl propanoate (isopropoxyphene),



and enantiomer

F. (2*RS*)-3-(dimethylamino)-2-methyl-1-phenylpropan-1-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

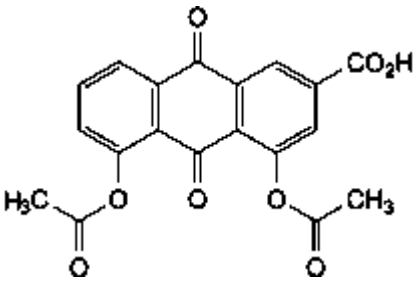
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diacerein

General Notices

(Ph. Eur. monograph 2409)



$C_{19}H_{12}O_8$ 368.3 *13739-02-1*

Action and use

Anti-inflammatory used in the treatment of arthritis and osteoarthritis.

Ph Eur

DEFINITION

4,5-Bis(acetyloxy)-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, soluble in dimethylacetamide, slightly soluble in tetrahydrofuran, practically insoluble in anhydrous ethanol.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *diacerein CRS*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Impurities B and H

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solution A Dissolve 10 g of sodium hydroxide R in 500 mL of water R.

Solution B Dissolve 14.7 g of sodium chloride R and 18.8 g of glycine R in 500 mL of water R.

Solution C Mix 25.3 volumes of solution A and 74.6 volumes of solution B. If necessary, adjust to pH 9.5 using dilute sodium hydroxide solution R or dilute sulfuric acid R.

Solution D Dilute 5 mL of dilute sulfuric acid R to 500 mL with water R.

Test solution Dissolve 0.100 g of the substance to be examined in 30 mL of solution A and mix for 10 min. Add 70 mL of solution B and adjust to pH 9.5 with dilute sodium hydroxide solution R or dilute sulfuric acid R, if necessary. Extract with 3 quantities, each of 25 mL, of methylene chloride R. Combine the methylene chloride extracts and wash with 2 quantities, each of 8 mL, of solution C and then once with 10 mL of solution D. Evaporate the organic layer to dryness at 33 °C, completing the drying procedure using compressed air. Dissolve the residue in 2.0 mL of the mobile phase.

Reference solution (a) Dissolve 7.5 mg of diacerein impurity B CRS in tetrahydrofuran R and dilute to 25.0 mL with the same solvent. Sonicate for not more than 30 s. Dilute 1.0 mL of the solution to 100.0 mL with solution A. Dilute 5.0 mL of this solution to 50.0 mL with solution A. Mix 5.0 mL of this solution with 25 mL of solution A for 10 min. Add 70 mL of solution B and adjust to pH 9.5 with dilute sodium hydroxide solution R or dilute sulfuric acid R, if necessary. Perform the extraction as described for the test solution. *Care should be taken that the time between dissolution of diacerein impurity B in tetrahydrofuran and extraction does not exceed 30 min.*

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 5.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: irregular octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 16 ± 1 °C.

Mobile phase tetrahydrofuran R, acetonitrile R, 4 g/L solution of citric acid monohydrate R (8:27.5:64.5 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 100 µL.

Run time 2.5 times the retention time of impurity B.

Retention time Impurity B = about 11 min.

www.webofpharma.com

https://thietbiuocngocanh.com/

System suitability Reference solution (b):

— *signal-to-noise ratio*: minimum 10 for the principal peak.

Limit:

— *sum of impurities B and H*: not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (a) (15 ppm).

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture Mobile phase A, mobile phase B (50:50 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in 50 mL of *tetrahydrofuran R* and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *tetrahydrofuran R*. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) In order to prepare impurities D and E *in situ*, add 10.0 mL of a 0.4 g/L solution of *sodium hydroxide R* to 0.100 g of the substance to be examined. Add 40 mL of *tetrahydrofuran R* and dilute to 100 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *diacerein impurity mixture CRS* (impurities C and F) in a mixture of 0.5 mL of *tetrahydrofuran R* and 0.5 mL of the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: to 353 mL of *water for chromatography R* add 147 mL of *phosphoric acid R* and mix; dilute 2 mL of the solution to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	80	20
3 - 13	80 → 60	20 → 40

www.webofpharma.com

https://thietbiuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
13 - 20	60	40

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *diacerein impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C and F; use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities D and E.

Relative retention With reference to diacerein (retention time = about 13.5 min): impurity D = about 1.1; impurity E = about 1.15; impurity C = about 1.2; impurity F = about 1.3.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurities D and E in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 100 for the principal peak in the chromatogram obtained with reference solution (a).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.4; impurity D = 1.3; impurity E = 1.3; impurity F = 9.5;

— *impurities D, E*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity F*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 20 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Test solution Dissolve 60.0 mg of the substance to be examined in *tetrahydrofuran R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 25.0 mL with the solvent mixture.

Reference solution Dissolve 60.0 mg of *diacerein CRS* in *tetrahydrofuran R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 25.0 mL with the solvent mixture.

Calculate the percentage content of $C_{19}H_{12}O_8$ taking into account the assigned content of *diacerein CRS*.

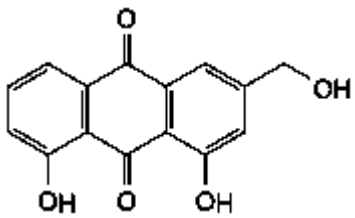
STORAGE

In an airtight container, protected from light.

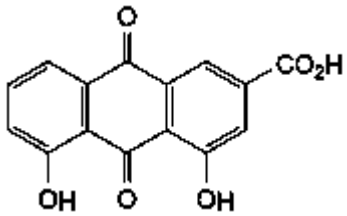
IMPURITIES

Specified impurities *B, C, D, E, F, H.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G.*



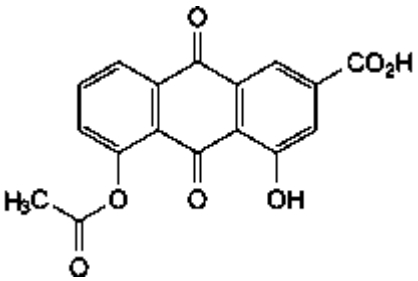
B. 1,8-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione (aloe-emodin),



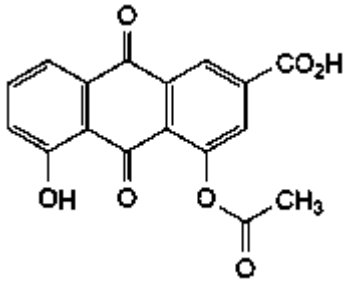
C. 4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (rhein),

www.webofpharma.com

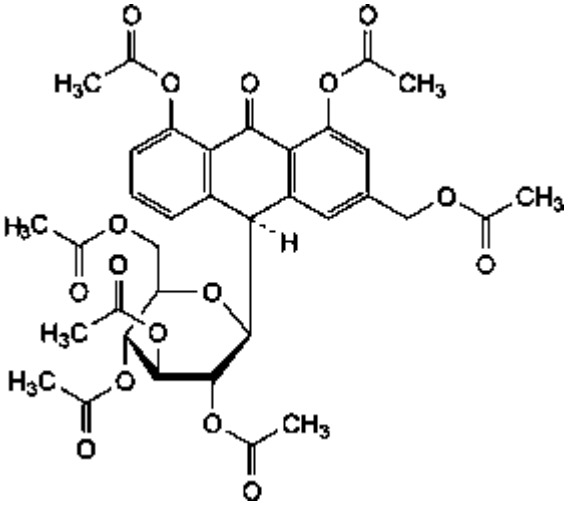
https://thuocngocanh.com/



D. 5-(acetyloxy)-4-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (monoacetyl rhein isomer A),



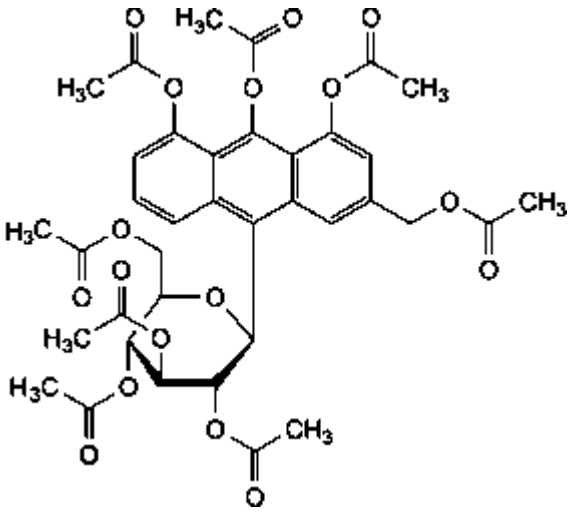
E. 4-(acetyloxy)-5-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (monoacetyl rhein isomer B),



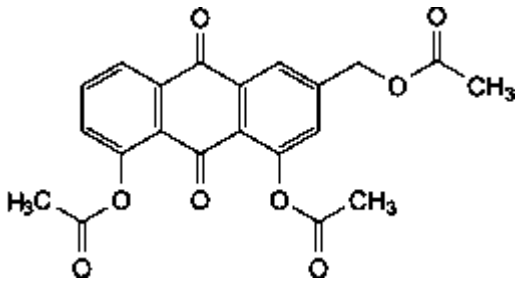
F. (10*S*)-3-[(acetyloxy)methyl]-10-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-9-oxo-9,10-dihydroanthracene-1,8-diyl diacetate (heptaacetyl aloin, heptaacetyl barbaloin),

www.webofpharma.com

https://thuocngocanh.com/



G. 3-[(acetyloxy)methyl]-10-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)anthracene-1,8,9-triyl triacetate,



H. 3-[(acetyloxy)methyl]-9,10-dioxo-9,10-dihydroanthracene-1,8-diyl diacetate (triacetyl aloe-emodin).

Ph Eur

© Crown Copyright 2022

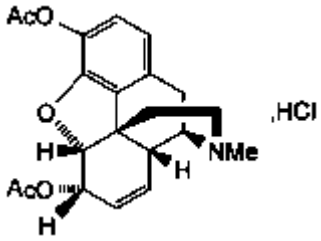
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diamorphine Hydrochloride

General Notices



$C_{21}H_{23}NO_5$,HCl,H_2O 423.9 *1502-95-0*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Bupivacaine and Diamorphine Injection

Diamorphine Tablets

Diamorphine Injection

DEFINITION

Diamorphine Hydrochloride is 4,5-epoxy-17-methylmorphinan-3,6-diyl diacetate hydrochloride monohydrate. It contains not less than 98.0% and not more than 102.0% of $C_{21}H_{23}NO_5$,HCl, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white, crystalline powder.

Freely soluble in *water*; soluble in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

A. Dissolve a sufficient quantity in the minimum volume of *dichloromethane* and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of diamorphine hydrochloride *(RS 093)*.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity

Dissolve 0.2 g in 10 mL of *carbon dioxide-free water* and titrate with *0.02M sodium hydroxide VS* using *methyl red solution* as indicator. Not more than 0.2 mL of *0.02M sodium hydroxide VS* is required.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.5% w/v of the substance being examined in *water*.

(2) Dilute 1 volume of solution (1) to 50 volumes with *water*.

(3) A freshly prepared solution containing 0.1% w/v of the substance being examined in 0.01M *sodium hydroxide*.

(4) Dilute 1 volume of solution (2) to 20 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *base-deactivated octylsilyl silica gel for chromatography*, (5 µm) (Lichrospher RP-select B is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 283 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of the peak due to diamorphine hydrochloride.

MOBILE PHASE

0.11 % w/v of *sodium octanesulfonate* in a mixture of 10 volumes of *glacial acetic acid*, 10 volumes of *methanol*, 115 volumes of *acetonitrile* and 365 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) exhibits two *secondary peaks* with retention times relative to the principal peak of about 0.23 (morphine) and 0.43 (6-*O*-acetyl-morphine);

in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to morphine and 6-*O*-acetyl-morphine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 6-*O*-acetylmorphine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the sum of the areas of any other *secondary peaks* is not greater than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

www.webofpharma.com

https://thietbiuocngocanh.com/

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Loss on drying

When dried to constant weight at 105°, loses 3.0 to 4.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

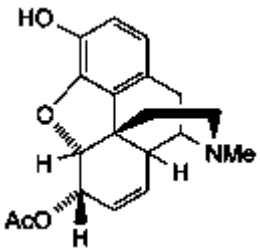
Dissolve 0.40 g in 50 mL of *ethanol (96%)* and add 5.0 mL of *0.01M hydrochloric acid VS*. Titrate with *0.1M sodium hydroxide VS* , determining the end point potentiometrically. Measure the volume of titrant required between the two points of inflection. Each mL of *0.1M sodium hydroxide VS* is equivalent to 40.59 mg of $C_{21}H_{23}NO_5$,HCl.

STORAGE

Diamorphine Hydrochloride should be protected from light.

IMPURITIES

The impurity limited by this monograph is:



A. 6-*O*-acetylmorphine.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diamorphine Injection

General Notices

Action and use

Opioid receptor agonist analgesic.

DEFINITION

Diamorphine Injection is a sterile solution of Diamorphine Hydrochloride in Water for Injections. It is prepared by dissolving Diamorphine Hydrochloride for Injection in the requisite amount of Water for Injections immediately before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Diamorphine Injection deteriorates on storage and should be used immediately after preparation.

DIAMORPHINE HYDROCHLORIDE FOR INJECTION

DEFINITION

Diamorphine Hydrochloride for Injection is a sterile material prepared from Diamorphine Hydrochloride with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of diamorphine hydrochloride, $C_{21}H_{23}NO_5,HCl,H_2O$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

Dissolve a sufficient quantity of the contents of the sealed container in the minimum volume of *dichloromethane* and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of diamorphine hydrochloride *(RS 093)*.

TESTS

6-*O*-Acetylmorphine

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions freshly prepared.

(1) Dissolve a quantity of the powder for injection containing 0.2 g of Diamorphine Hydrochloride in 10 mL of *water*.

(2) Dilute 1 volume of solution (1) to 20 volumes with *water*.

(3) Dilute 1 volume of solution (1) to 20 volumes with 0.01M *sodium hydroxide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP-select B is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 283 nm.

(f) Inject 20 µL of each solution.

When the chromatograms are recorded under the prescribed conditions, the retention time of diamorphine hydrochloride is about 20.3 minutes.

MOBILE PHASE

0.11% w/v of *sodium octanesulfonate* in a mixture of 10 volumes of *glacial acetic acid*, 10 volumes of *methanol*, 115 volumes of *acetonitrile* and 365 volumes of *water*.

SYSTEM SUITABILITY

The chromatogram obtained with solution (3) exhibits two *secondary peaks* with retention times relative to the principal peak of about 0.23 (morphine) and 0.43 (6-*O*-acetyl-morphine). The test is not valid unless the *resolution* between the peaks due to morphine and 6-*O*-acetyl-morphine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 6-*O*-acetylmorphine is not greater than the area of the peak in the chromatogram obtained with solution (2) (5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dissolve a quantity of the powder for injection containing 30 mg of Diamorphine Hydrochloride in 100 mL of *water* and filter.

(2) 0.03% w/v of *diamorphine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 260 nm.

(f) Inject 10 µL of each solution.

When the chromatograms are recorded under the prescribed conditions, the retention time of diamorphine hydrochloride is about 3.5 minutes.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of 0.01M *sodium heptanesulfonate*, containing 0.0075M N,N-*dimethyloctylamine*, which has been adjusted to pH 3.0 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

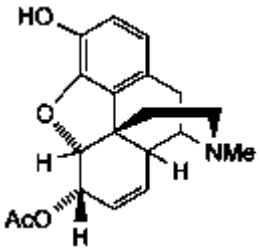
Calculate the content of $C_{21}H_{23}NO_5,HCl,H_2O$ in the injection using the declared content of $C_{21}H_{23}NO_5,HCl,H_2O$ in *diamorphine hydrochloride BPCRS*.

STORAGE

The sealed container should be protected from light.

IMPURITIES

The impurity limited by the requirements of this monograph is:



A. 6-*O*-Acetylmorphine.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://nhathuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diamorphine Tablets

General Notices

Action and use

Opioid receptor agonist analgesic.

DEFINITION

Diamorphine Tablets contain Diamorphine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diamorphine hydrochloride, $C_{21}H_{23}NO_5,HCl,H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 10 mg of Diamorphine Hydrochloride with 10 mL of *dichloromethane*, filter and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of diamorphine hydrochloride *(RS 093)*.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 15 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, to produce a solution expected to contain 0.0011% w/v of Diamorphine Hydrochloride.

(2) 0.0011% w/v of *diamorphine hydrochloride BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 260 nm.

(f) Inject 250 µL of each solution.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of 0.01M *sodium heptanesulfonate*, containing 0.0075M N,N-*dimethyloctylamine*, which has been adjusted to pH 3.0 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of $C_{21}H_{23}NO_5,HCl,H_2O$ in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{23}NO_5,HCl,H_2O$ in *diamorphine hydrochloride BPCRS*.

LIMITS

The amount of diamorphine hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity powdered tablets containing 80 mg of Diamorphine Hydrochloride in 10 mL of *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(3) Disperse a quantity of the powdered tablets to give a solution containing 0.1% w/v of Diamorphine Hydrochloride in 0.01M *sodium hydroxide*; the solution should be freshly prepared.

(4) Dilute 1 volume of solution (2) to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP-select B is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 283 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice the retention time of the peak due to diamorphine.

MOBILE PHASE

0.11% w/v of *sodium octanesulfonate* in a mixture of 10 volumes of *glacial acetic acid*, 10 volumes of *methanol*, 115 volumes of *acetonitrile* and 365 volumes of *water*.

www.webofpharma.com

https://thuocngocanh.com/

When the chromatograms are recorded under the prescribed conditions the retention time of diamorphine is about 20 minutes.

SYSTEM SUITABILITY

The chromatogram obtained with solution (3) exhibits two *secondary peaks* with retention times relative to the principal peak of about 0.23 (morphine) and 0.43 (6-*O*-acetyl-morphine). The test is not valid unless the *resolution* between the peaks due to morphine and 6-*O*-acetyl-morphine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 6-*O*-acetylmorphine is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any other *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 30 mg of Diamorphine Hydrochloride in *water*, dilute to 100 mL with *water*.
(2) 0.03% w/v of *diamorphine hydrochloride BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 10 µL.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of 0.01M *sodium heptanesulfonate*, containing 0.0075M N,N-*dimethyloctylamine*, which has been adjusted to pH 3.0 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{23}NO_5$,HCl,H_2O in the tablets using the declared content of $C_{21}H_{23}NO_5$,HCl,H_2O in *diamorphine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph those listed under Diamorphine Hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

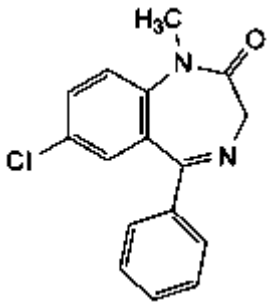
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diazepam

General Notices

(Ph. Eur. monograph 0022)



$C_{16}H_{13}ClN_2O$ 284.7 *439-14-5*

Action and use

Benzodiazepine.

Preparations

Diazepam Injection

Diazepam Oral Solution

Diazepam Rectal Solution

Diazepam Tablets

Ph Eur

DEFINITION

7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison: *diazepam CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions protected from bright light.*

Test solution Dissolve 25.0 mg of the substance to be examined in 0.5 mL of *acetonitrile R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *diazepam for system suitability CRS* (containing impurities A, B and E) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 22 volumes of *acetonitrile R*, 34 volumes of *methanol R* and 44 volumes of a 3.4 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with *dilute sodium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time About 4 times the retention time of diazepam.

Identification of impurities Use the chromatogram supplied with *diazepam for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and E.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to diazepam (retention time = about 9 min): impurity E = about 0.7; impurity A = about 0.8; impurity B = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurities E and A and minimum 6.0 between the peaks due to impurity A and diazepam.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.3; impurity E = 1.3;

— *impurities A, B, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 28.47 mg of $C_{16}H_{13}ClN_2O$.

STORAGE

Protected from light.

IMPURITIES

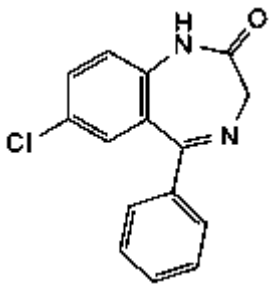
Specified impurities *A, B, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

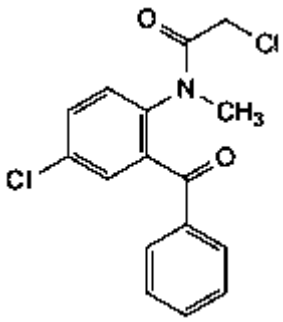
www.webofpharma.com

https://thuocngocanh.com/

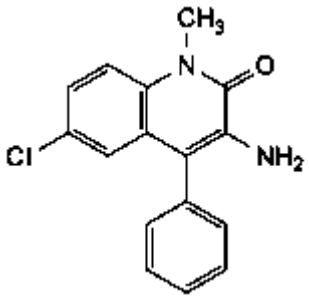
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, F.



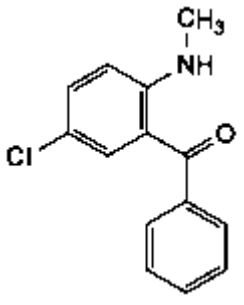
A. 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (nordazepam),



B. *N*-(2-benzoyl-4-chlorophenyl)-2-chloro-*N*-methylacetamide,



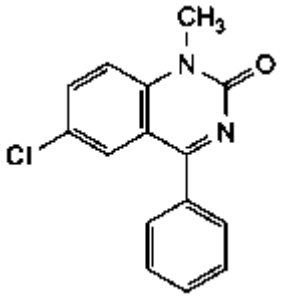
C. 3-amino-6-chloro-1-methyl-4-phenylquinolin-2(1*H*)-one,



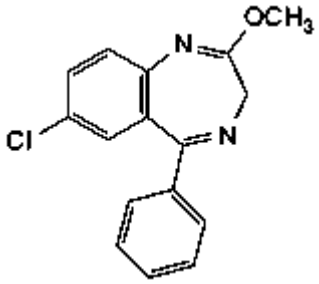
D. [5-chloro-2-(methylamino)phenyl]phenylmethanone,

www.webofpharma.com

https://thuocngocanh.com/



E. 6-chloro-1-methyl-4-phenylquinazolin-2(1*H*)-one,



F. 7-chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diazepam Injection

General Notices

Action and use

Benzodiazepine.

DEFINITION

Diazepam Injection is a sterile solution of Diazepam in Water for Injections or other suitable solvent.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of diazepam, $C_{16}H_{13}ClN_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, of the solution obtained in the Assay exhibits a maximum at 368 nm.

B. Complies with test B for Identification described under Diazepam Tablets applying separately to the plate 10 µL of each of the following solutions. For solution (1) dilute a suitable volume of the injection with sufficient *methanol* to produce a solution containing 0.10% w/v of Diazepam. Solution (2) contains 0.10% w/v of *diazepam BPCRS* in *methanol*.

TESTS

Acidity or alkalinity

pH, 6.2 to 7.0, Appendix V L.

ASSAY

To a volume containing 10 mg of Diazepam add 20 mL of *mixed phosphate buffer pH 7.0* and extract with four 20 mL quantities of *chloroform*, passing each extract through the same 5 g of *anhydrous sodium sulfate*. Combine the chloroform extracts, dilute to 100 mL with *chloroform* and mix. Evaporate 10 mL to dryness in a current of nitrogen, dissolve the residue in 25 mL of 0.05M *methanolic sulfuric acid*, mix and measure the *absorbance* of the resulting solution at the maximum at 368 nm, Appendix II B. Calculate the content of $C_{16}H_{13}ClN_2O$ taking 151 as the value of A(1%, 1 cm) at the maximum at 368 nm.

STORAGE

Diazepam Injection should be protected from light.

www.webofpharma.com

https://thuathuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diazepam Oral Solution

General Notices

Action and use

Benzodiazepine.

DEFINITION

Diazepam Oral Solution is a solution of Diazepam in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of diazepam, $C_{16}H_{13}ClN_2O$

95.0 to 115.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 320 to 400 nm of the final solution obtained in the Assay exhibits a maximum at 368 nm. The *light absorption* in the range 230 to 330 nm of a solution prepared by diluting 1 volume of the final solution obtained in the Assay to 5 volumes with 0.1M *methanolic sulfuric acid* exhibits two maxima, at 243 nm and 286 nm.

B. Carry out the method described under Related substances applying separately to the plate 10 µL of each of solution (1) and solution (2) and using as solution (2) a 0.4% w/v solution of *diazepam BPCRS* in *ethanol (96%)*. After removal of the plate, allow the solvent to evaporate and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 6.6, Appendix V L.

Related substances

Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of equal volumes of *ethyl acetate* and *hexane* as the mobile phase but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 25 µL of each of the following solutions. For solution (1) add 40 mL of *water* to a volume of the oral solution containing 8 mg of Diazepam and extract with three 50-mL quantities of *ether*. Wash the combined ether extracts with 30 mL of 1M *sodium hydroxide* followed by two 40 mL quantities of *water*. Shake the extract with *anhydrous sodium sulfate*, filter, evaporate to dryness and dissolve the residue in 2 mL of *ethanol (96%)*. Solution (2) contains 0.0080% w/v of *5-chloro-2-methylaminobenzophenone BPCRS* in *ethanol (96%)*. Solution (3) contains 0.0040% w/v of *3-amino-6-chloro-1-methyl-4-phenylquinolin-2-ol BPCRS* in *ethanol (96%)*. For

www.webofpharma.com

https://thuocngocanh.com/

solution (4) dilute 2 mL of solution (1) to 100 mL with *ethanol (96%)* and dilute 1 mL of the resulting solution to 10 mL with the same solvent. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to 5-chloro-2-methylaminobenzophenone is not more intense than the spot in the chromatogram obtained with solution (2) and any spot corresponding to 3-amino-6-chloro-1-methyl-4-phenylquinolin-2-ol is not more intense than the spot in the chromatogram obtained with solution (3). Any other *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4).

ASSAY

To a weighed quantity containing 1 mg of Diazepam add 25 mL of a mixture of equal volumes of 1M *sodium hydroxide* and *methanol* and shake for 2 minutes. Extract with five 25 mL quantities of *chloroform*, shaking for 2 minutes each time. Combine the chloroform extracts, shake with 5 g of *anhydrous sodium sulfate* and filter. Evaporate to dryness, dissolve the residue in 25 mL of 0.1M *methanolic sulfuric acid* and filter. Measure the *absorbance* of the filtrate, Appendix II B, at the maximum at 368 nm. Calculate the content of $C_{16}H_{13}ClN_2O$ taking 151 as the value of A(1%, 1 cm) at the maximum at 368 nm. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{16}H_{13}ClN_2O$, weight in volume.

STORAGE

Diazepam Oral Solution should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diazepam Rectal Solution

General Notices

Action and use

Benzodiazepine.

DEFINITION

Diazepam Rectal Solution is a solution of Diazepam in a suitable vehicle.

The rectal solution complies with the requirements stated under Rectal Preparations and with the following requirements.

Content of diazepam, $C_{16}H_{13}ClN_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, of the solution obtained in the Assay exhibits a maximum at 368 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 10 volumes of *methanol* and 100 volumes of *chloroform* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) dilute a suitable volume of the rectal solution with sufficient *methanol* to produce a solution containing 0.10% w/v of Diazepam. Solution (2) contains 0.10% w/v of *diazepam BPCRS* in *methanol*. After removal of the plate, spray it with a 10% v/v solution of *sulfuric acid* in *absolute ethanol*, heat at 105° for 10 minutes and examine under *ultraviolet light (365 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.2 to 7.2, Appendix V L.

ASSAY

To a volume containing 10 mg of Diazepam add 20 mL of *mixed phosphate buffer pH 7.0* and extract with four 20 mL quantities of *chloroform*, passing each extract through the same 5 g of *anhydrous sodium sulfate*. Combine the chloroform extracts, dilute to 100 mL with *chloroform* and mix. Evaporate 10 mL to dryness in a current of nitrogen, dissolve the residue in 25 mL of 0.05M *methanolic sulfuric acid*, mix and measure the *absorbance* of the resulting solution at the maximum at 368 nm, Appendix II B. Calculate the content of $C_{16}H_{13}ClN_2O$ taking 151 as the value of A(1%, 1 cm) at the maximum at 368 nm.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

Diazepam Rectal Solution should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diazepam Tablets

General Notices

Action and use

Benzodiazepine.

DEFINITION

Diazepam Tablets contain Diazepam.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diazepam, $C_{16}H_{13}ClN_2O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits two maxima, at 242 nm and 284 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Shake a quantity of the powdered tablets with sufficient solvent to produce a solution containing 0.50% w/v of Diazepam, allow to settle and decant the supernatant liquid.

(2) 0.5% w/v of *diazepam BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, spray it with a 10% v/v solution of *sulfuric acid* in *absolute ethanol*, heat at 105° for 10 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

10 volumes of *methanol* and 100 volumes of *chloroform*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Related substances and decomposition products

Carry out the procedure in subdued light. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *ethanol (96%)*.

(1) Shake a quantity of the powdered tablets containing 50 mg of Diazepam with 5 mL of solvent, filter and use immediately.

(2) Dilute 1 volume of solution (1) to 50 volumes and use immediately.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of solution (1) and 5 µL of solution (2).

(d) Develop the plate to 12 cm.

(e) After removal of the plate, allow the solvent to evaporate and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

Equal volumes of *ethyl acetate* and *hexane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted with *0.1M hydrochloric acid* if necessary, at the maximum at 286 nm, Appendix II B using *0.1M hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of diazepam, $C_{16}H_{13}ClN_2O$, in the medium taking 488 as the value of A(1%, 1 cm) at the maximum at 286 nm.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Diazepam comply with the requirement stated under Tablets using the following method of analysis. To one tablet add 1 mL of *water*, allow the tablet to disintegrate and stand for 15 minutes. Add 80 mL of a 0.5% w/v solution of *sulfuric acid* in *methanol*, shake for 15 minutes, add sufficient of the methanolic sulfuric acid to produce 100 mL and

www.webofpharma.com

https://thuocngocanh.com/

filter. Measure the *absorbance* of the filtrate at the maximum at 284 nm, Appendix II B. Calculate the content of $C_{16}H_{13}ClN_2O$ taking 450 as the value of A(1%, 1 cm) at the maximum at 284 nm.

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 10 mg of Diazepam add 5 mL of *water*, mix and allow to stand for 15 minutes. Add 70 mL of a 0.5% w/v solution of *sulfuric acid* in *methanol*, shake for 15 minutes, add sufficient of the methanolic sulfuric acid to produce 100 mL and filter. Dilute 10 mL of the filtrate to 50 mL with the same solvent and measure the *absorbance* of the resulting solution at the maximum at 284 nm, Appendix II B. Calculate the content of $C_{16}H_{13}ClN_2O$ taking 450 as the value of A(1%, 1 cm) at the maximum at 284 nm.

STORAGE

Diazepam Tablets should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

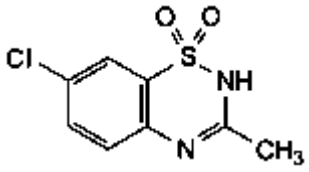
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Diazoxide

General Notices

(Ph. Eur. monograph 0550)



$C_8H_7ClN_2O_2S$ 230.7 *364-98-7*

Action and use

Vasodilator; Treatment of hypertension.

Preparations

Diazoxide Injection

Diazoxide Tablets

Ph Eur

DEFINITION

Diazoxide contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of 7-chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, fine or crystalline powder, practically insoluble in water, freely soluble in dimethylformamide, slightly soluble in ethanol (96 per cent). It is very soluble in dilute solutions of the alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Dissolve 50.0 mg in 5 mL of *1 M sodium hydroxide* and dilute to 50.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *0.1 M sodium hydroxide*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 280 nm and a shoulder at 304 nm. The specific absorbance at the maximum is 570 to 610.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *diazoxide CRS*. Examine the substances prepared as discs using *potassium bromide R*.

C. Examine the chromatograms obtained in the test for related substances in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (b).

D. Dissolve about 20 mg in a mixture of 5 mL of *hydrochloric acid R* and 10 mL of *water R*. Add 0.1 g of *zinc powder R*. Boil for 5 min, cool and filter. To the filtrate add 2 mL of a 1 g/L solution of *sodium nitrite R* and mix. Allow to stand for 1 min and add 1 mL of a 5 g/L solution of *naphthylethylenediamine dihydrochloride R*. A red or violet-red colour develops.

TESTS

Appearance of solution

Dissolve 0.4 g in 2 mL of *1 M sodium hydroxide* and dilute to 20 mL with *water R*. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Acidity or alkalinity

To 0.5 g of the powdered substance to be examined add 30 mL of *carbon dioxide-free water R*, shake for 2 min and filter. To 10 mL of the filtrate add 0.2 mL of *0.01 M sodium hydroxide* and 0.15 mL of *methyl red solution R*. The solution is yellow. Not more than 0.4 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution (a) Dissolve 0.1 g of the substance to be examined in a mixture of 0.5 mL of *1 M sodium hydroxide* and 1 mL of *methanol R* and dilute to 5 mL with *methanol R*.

Test solution (b) Dilute 1 mL of test solution (a) to 5 mL with a mixture of 1 volume of *1 M sodium hydroxide* and 9 volumes of *methanol R*.

Reference solution (a) Dilute 0.5 mL of test solution (a) to 100 mL with a mixture of 1 volume of *1 M sodium hydroxide* and 9 volumes of *methanol R*.

Reference solution (b) Dissolve 20 mg of *diazoxide CRS* in a mixture of 0.5 mL of *1 M sodium hydroxide* and 1 mL of *methanol R* and dilute to 5 mL with *methanol R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 15 cm using a mixture of 7 volumes of *concentrated ammonia R*, 25 volumes of *methanol R* and 68 volumes of *chloroform R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g with gentle heating in 50 mL of a mixture of 1 volume of *water R* and 2 volumes of *dimethylformamide R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 23.07 mg of $C_8H_7ClN_2O_2S$.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diazoxide Injection

General Notices

Action and use

Vasodilator; treatment of hypertension.

DEFINITION

Diazoxide Injection is a sterile solution of Diazoxide in Water for Injections, prepared with the aid of Sodium Hydroxide.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of diazoxide, $C_8H_7ClN_2O_2S$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

To a volume containing 0.3 g of Diazoxide add 2 mL of 2M *hydrochloric acid*, stir, filter the precipitate and wash the filter thoroughly with *water* until the filtrate is free from acid. The precipitate, after drying at 105°, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of diazoxide *(RS 094)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.001% w/v solution in 0.1M *sodium hydroxide* exhibits a maximum only at 280 nm.

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the injection, diluted if necessary, with *methanol* to contain 0.02% w/v of Diazoxide.

(2) 0.02% w/v of *diazoxide EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air until the solvent has evaporated, examine under *ultraviolet light (254 nm)* and then treat the plate by *Method I* and examine again.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

20 volumes of *acetone*, 30 volumes of *ether* and 50 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH, 11.2 to 11.9, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the injection diluted, if necessary, with 0.1M *sodium hydroxide* to contain 1.5% w/v of Diazoxide.

(2) Dilute 1 volume of solution (1) to 200 volumes with 0.1M *sodium hydroxide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

7 volumes of 18M *ammonia*, 25 volumes of *methanol* and 68 volumes of *chloroform*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

To a volume containing 75 mg of Diazoxide add sufficient 0.1M *sodium hydroxide* to produce 500 mL. Dilute 5 mL to 100 mL with 0.1M *sodium hydroxide* and measure the *absorbance* of the resulting solution at the maximum at 280 nm, Appendix II B. Calculate the content of $C_8H_7ClN_2O_2S$ taking 585 as the value of A(1%, 1 cm) at the maximum at 280 nm.

STORAGE

Diazoxide Injection should be protected from light.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diazoxide Tablets

General Notices

Action and use

Vasodilator; treatment of hypertension.

DEFINITION

Diazoxide Tablets contain Diazoxide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diazoxide, $C_8H_7ClN_2O_2S$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.2 g of Diazoxide with 50 mL of *absolute ethanol*, filter and evaporate the filtrate to dryness at a pressure of 2 kPa. The residue complies with the following tests.

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.001% w/v solution in 0.1M *sodium hydroxide* exhibits a maximum only at 280 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) 0.02% w/v of the residue in *methanol*.

(2) 0.02% w/v of *diazoxide EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use *silica gel* GF_{254} as the coating.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air until the solvent has evaporated, examine under *ultraviolet light (254 nm)* and then treat the plate by *Method I* and examine again.

MOBILE PHASE

20 volumes of *acetone*, 30 volumes of *ether*, and 50 volumes of *toluene*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in colour and intensity to that in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.75 g of Diazoxide with 40 mL of 0.1M *sodium hydroxide* for 30 minutes, filter and dilute the filtrate to 50 mL with 0.1M *sodium hydroxide*.

(2) Dilute 1 volume of solution (1) to 200 volumes with 0.1M *sodium hydroxide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use *a TLC silica gel* GF_{254} *plate*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

7 volumes of 18M *ammonia*, 25 volumes of *methanol* and 68 volumes of *chloroform*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 50 mg of Diazoxide add 70 mL of *methanol*, shake for 1 hour, add sufficient *methanol* to produce 100 mL, mix and filter. Dilute 5 mL of the filtrate to 250 mL with 0.1M *sodium hydroxide* and measure the *absorbance* of the resulting solution at the maximum at 280 nm, Appendix II B. Calculate the content of $C_8H_7ClN_2O_2S$ taking 585 as the value of A(1%, 1 cm) at the maximum at 280 nm.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

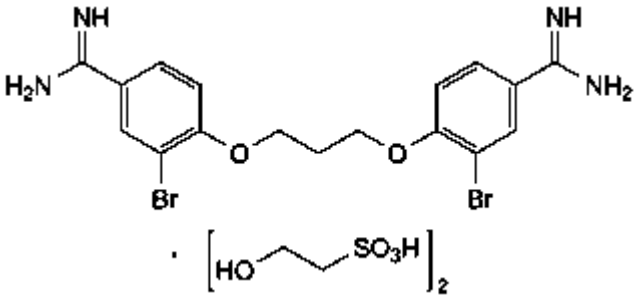
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dibrompropamidine Isetionate

General Notices

(Dibrompropamidine Diisetionate, Ph. Eur. monograph 2300)



$C_{21}H_{30}Br_2N_4O_{10}S_2$ 722 *614-87-9*

Action and use

Antiseptic.

Ph Eur

DEFINITION

3,3′-Dibromo-4,4′-[propane-1,3-diylbis(oxy)]dibenzimidamide bis(2-hydroxyethanesulfonate).

Content

99.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

It is considered that alkyl 2-hydroxyethanesulfonate esters are potential impurities in dibrompropamidine diisetionate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation including, where necessary, demonstration that alkyl 2-hydroxyethanesulfonate esters are not detectable in the final product.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

https://thuocngocanh.com/

Freely soluble or soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *dibrompropamidine diisetionate CRS*.

B. Mix 0.1 g with 0.5 g of *anhydrous sodium carbonate R*, ignite and take up the residue with 20 mL of *water R*. Filter and neutralise the filtrate to *blue litmus paper R* with *nitric acid R*. The filtrate gives reaction (a) of bromides (2.3.1).

TESTS

pH (2.2.3)

5.0 to 6.0.

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *anhydrous formic acid R*, *methanol R*, *ethyl acetate R* (0.01:8:12 *V/V/V*).

Test solution To 8 mL of *methanol R* add 20.0 mg of the substance to be examined and dissolve with the aid of an ultrasonic bath. Add 11 mL of *ethyl acetate R* then 10 µL of *anhydrous formic acid R* and mix. Dilute to 20.0 mL with *ethyl acetate R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *dibrompropamidine for system suitability CRS* (containing impurities A and B) in 4 mL of *methanol R* using an ultrasonic bath. Add 5 mL of *ethyl acetate R*, then 5 µL of *anhydrous formic acid R* and mix. Dilute to 10.0 mL with *ethyl acetate R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *strong cation-exchange silica gel for chromatography R* (5 µm).

Mobile phase Mix 4 volumes of a 25 g/L solution of *ammonium formate R* in *methanol R* and 6 volumes of *ethyl acetate R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 40 µL.

www.webofpharma.com

https://thuocngocanh.com/

Run time 1.5 times the retention time of dibrompropamidine.

Identification of impurities Use the chromatogram supplied with *dibrompropamidine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to dibrompropamidine (retention time = about 20 min): impurity A = about 0.4; impurity B = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to dibrompropamidine.

Limits:

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *dimethylformamide R*. Titrate with 0.1 M tetrabutylammonium hydroxide under a current of *nitrogen R*, determining the end-point potentiometrically (*2.2.20*).

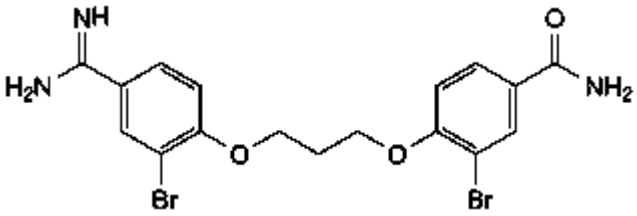
1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 36.12 mg of $C_{21}H_{30}Br_2N_4O_{10}S_2$.

IMPURITIES

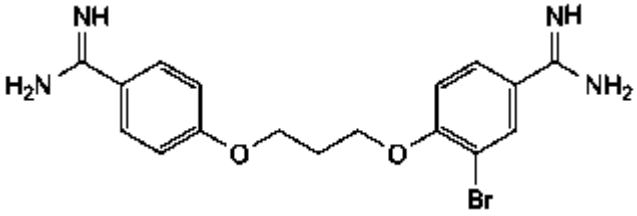
Specified impurities *A, B.*

www.webofpharma.com

https://thuocngocanh.com/



A. 3-bromo-4-[3-(2-bromo-4-carbamimidoylphenoxy)propoxy]benzamide,



B. 3-bromo-4-[3-(4-carbamimidoylphenoxy)propoxy]benzimidamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

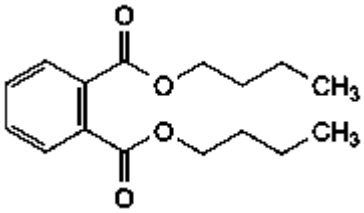
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dibutyl Phthalate

General Notices

(Ph. Eur. monograph 0762)



$C_{16}H_{22}O_4$ 278.3 *84-74-2*

Action and use

Insect repellent.

Ph Eur

DEFINITION

Dibutyl benzene-1,2-dicarboxylate.

Content

99.0 per cent *m/m* to 101.0 per cent *m/m*.

CHARACTERS

Appearance

Clear, oily liquid, colourless or very slightly yellow.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, D, E.

www.webofpharma.com

https://thietbiuocngocanh.com/

A. Relative density (2.2.5): 1.043 to 1.048.

B. Refractive index (2.2.6): 1.490 to 1.495.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *dibutyl phthalate CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *ether R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 50 mg of *dibutyl phthalate CRS* in *ether R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *heptane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

E. To about 0.1 mL add 0.25 mL of *sulfuric acid R* and 50 mg of *resorcinol R*. Heat in a water-bath for 5 min. Allow to cool. Add 10 mL of *water R* and 1 mL of *strong sodium hydroxide solution R*. The solution becomes yellow or brownish-yellow and shows a green fluorescence.

TESTS

Appearance

The substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Acidity

Dissolve 20.0 g in 50 mL of *ethanol (96 per cent) R* previously neutralised to *phenolphthalein solution R1*. Add 0.2 mL of *phenolphthalein solution R1*. Not more than 0.50 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances

Gas chromatography (2.2.28).

Internal standard solution Dissolve 60 mg of *bibenzyl R* in *methylene chloride R* and dilute to 20 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20.0 mL with the same solvent.

Test solution (b) Dissolve 1.0 g of the substance to be examined in *methylene chloride R*, add 2.0 mL of the internal standard solution and dilute to 20.0 mL with *methylene chloride R*.

Reference solution To 1.0 mL of test solution (a) add 10.0 mL of the internal standard solution and dilute to 100.0 mL with *methylene chloride R*.

Column:

— *material*: glass;

— *size*: *l* = 1.5 m, Ø = 4 mm;

— *stationary phase*: *silanised diatomaceous earth for gas chromatography R* (150-180 µm) impregnated with 3 per cent *m/m* of *phenyl(50)methyl(50)polysiloxane R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 190 °C;

— *injection port and detector*: 225 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time 3 times the retention time of dibutyl phthalate.

Elution order Bibenzyl, dibutyl phthalate.

Retention time Dibutyl phthalate = about 12 min.

System suitability:

— *resolution*: minimum 12 between the peaks due to bibenzyl and dibutyl phthalate in the chromatogram obtained with the reference solution;

— in the chromatogram obtained with test solution (a), there is no peak with the same retention time as the internal standard.

Limit:

— *total*: calculate the ratio (*R*) of the area of the peak due to dibutyl phthalate to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with test solution (b), calculate the ratio of the

www.webofpharma.com

https://thuocngocanh.com/

sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than *R* (1.0 per cent).

Water (*2.5.12*)

Maximum 0.2 per cent, determined on 10.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Introduce 0.750 g into a 250 mL borosilicate glass flask. Add 25.0 mL of *0.5 M alcoholic potassium hydroxide* and a few glass beads. Heat in a water-bath under a reflux condenser for 1 h. Add 1 mL of *phenolphthalein solution R1* and titrate immediately with *0.5 M hydrochloric acid* until the colour changes from red to colourless. Carry out a blank titration. Calculate the volume of potassium hydroxide used in the saponification.

1 mL of *0.5 M alcoholic potassium hydroxide* is equivalent to 69.59 mg of $C_{16}H_{22}O_4$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Dichloromethane

General Notices

(Methylene Chloride, Ph. Eur. monograph 0932)

CH_2Cl_2 84.9 *75-09-2*

Action and use

Excipient.

Ph Eur

DEFINITION

Dichloromethane.

It may contain maximum 2.0 per cent *V/V* of anhydrous ethanol and/or maximum 0.03 per cent *V/V* of 2-methylbut-2-ene as stabiliser.

CHARACTERS

Appearance

Clear, colourless, volatile liquid.

Solubility

Sparingly soluble in water, miscible with ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, D, E.

A. Relative density (see Tests).

B. Refractive index (see Tests).

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Films.

www.webofpharma.com

https://thuocngocanh.com/

Comparison *Ph. Eur. reference spectrum of methylene chloride*.

D. Heat 2 mL with 2 g of *potassium hydroxide R* and 20 mL of *ethanol (96 per cent) R* under a reflux condenser for 30 min. Allow to cool. Add 15 mL of *dilute sulfuric acid R* and filter. To 1 mL of the filtrate add 1 mL of a 15 g/L solution of *chromotropic acid, sodium salt R*, 2 mL of *water R* and 8 mL of *sulfuric acid R*. A violet colour is produced.

E. 2 mL of the filtrate obtained in identification test D gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance

It is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity

To 50 mL of *methanol R* previously neutralised to 0.1 mL of *bromothymol blue solution R1*, add 50 g of the substance to be examined. Not more than 0.15 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

Relative density (*2.2.5*)

1.320 to 1.332.

Refractive index (*2.2.6*)

1.423 to 1.425.

Ethanol, 2-methylbut-2-ene and volatile impurities

Gas chromatography (*2.2.28*).

Test solution The substance to be examined.

Reference solution (a) Dilute 100 µL of *carbon tetrachloride R* (impurity A), 500 µL of *chloroform R* (impurity B), 3.0 mL of *2-methylbut-2-ene R* and 5.0 mL of *methanol R* (impurity D) to 100.0 mL with the test solution.

Reference solution (b) Dilute 2.0 mL of *anhydrous ethanol R* and 1.0 mL of reference solution (a) to 100.0 mL with the test solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 1.8 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 1.0 mL/min, constant flow.

www.webofpharma.com

https://thuocngocanh.com/

Split ratio 1:40.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	40
	5 - 12.5	40 → 55
	12.5 - 18	55 → 100
	18 - 20	100
Injection port		260
Detector		300

Detection Flame ionisation; make-up gas flow rate: 25 mL/min.

Injection 2 µL of the test solution and reference solution (b).

Relative retention With reference to methylene chloride (retention time = about 7 min): impurity D = about 0.6; ethanol = about 0.8; 2-methylbut-2-ene = about 0.9; impurity B = about 1.7; impurity A = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to ethanol and 2-methylbut-2-ene;

— *signal-to-noise ratio*: minimum 5 for the peak due to impurity A.

Calculation of percentage contents:

— for ethanol, 2-methylbut-2-ene and impurities A and B, use the respective concentration of these substances in reference solution (b); correct the areas of the peaks in the chromatogram obtained with reference solution (b) by subtracting the area of the corresponding peak in the chromatogram obtained with the test solution;

— for any other impurity, use the concentration of impurity D in reference solution (b); correct the area of the peak due to impurity D in the chromatogram obtained with reference solution (b) by subtracting the area of the corresponding peak in the chromatogram obtained with the test solution.

Limits:

— *ethanol*: maximum 2.0 per cent *V/V*;

— *2-methylbut-2-ene*: maximum 300 ppm *V/V*;

— *impurity A*: maximum 10 ppm *V/V*;

www.webofpharma.com

https://thuocngocanh.com/

— *impurity B*: maximum 50 ppm *V/V*;

— *sum of impurities other than ethanol and 2-methylbut-2-ene*: maximum 0.1 per cent *V/V*;

— *reporting threshold*: 50 ppm *V/V*; the reporting threshold does not apply to impurity A.

Free chlorine

Place 5 mL in a ground-glass-stoppered tube. Add 5 mL of a 100 g/L solution of *potassium iodide R* and 0.2 g of *soluble starch R*. Shake for 30 s and allow to stand for 5 min. No blue colour develops.

Residue on evaporation

Maximum 20 ppm.

Evaporate 50.0 g to dryness on a water-bath and dry at 100-105 °C for 30 min. The residue weighs a maximum of 1 mg.

Water (*2.5.32*)

Maximum 0.02 per cent *m/m*, determined on 10.00 g.

STORAGE

In an airtight container, protected from light.

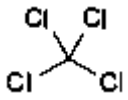
LABELLING

The label states the name and concentration of any stabilisers.

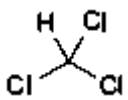
IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*



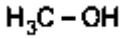
A. carbon tetrachloride,



B. trichloromethane (chloroform),

www.webofpharma.com

https://thuocngocanh.com/



D. methanol.

Ph Eur

© Crown Copyright 2022

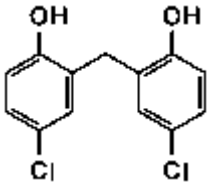
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dichlorophen

General Notices



$C_{13}H_{10}Cl_2O_2$ 269.1 *97-23-4*

Action and use

Antihelminthic.

Preparation

Dichlorophen Tablets

DEFINITION

Dichlorophen is 4,4′-dichloro-2,2′-methylenediphenol. It contains not less than 97.0% and not more than 101.0% of $C_{13}H_{10}Cl_2O_2$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or not more than slightly cream powder.

Practically insoluble in *water*; very soluble in *ether*; freely soluble in *ethanol (96%)*.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 220 to 350 nm of a 0.002% w/v solution in 0.1M *sodium hydroxide* exhibits two maxima, at 245 nm and 304 nm. The *absorbances* at the maxima are about 1.3 and about 0.54, respectively.

B. Dissolve 0.2 g in a mixture of 5 mL of *water* and 5 mL of 5M *sodium hydroxide*, cool in ice and add a solution prepared by mixing 1 mL of *sodium nitrite solution* with a cold solution containing 0.15 mL of *aniline* in a mixture of 4 mL of *water* and 1 mL of *hydrochloric acid*. A reddish brown precipitate is produced.

C. Fuse 0.5 g with 2 g of *anhydrous sodium carbonate*, cool, extract the residue with *water* and filter. The filtrate yields reaction A characteristic of *chlorides*, Appendix VI.

D. *Melting point*, about 175°, Appendix V A.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Chloride

Dissolve 1.0 g in 2 mL of *ethanol (96%)*, dilute to 100 mL with *water*, allow to stand for 5 minutes and filter through a slow filter paper (Whatman No. 42 is suitable). 15 mL of the filtrate complies with the *limit test for chlorides*, Appendix VII (350 ppm).

Sulfate

Shake 0.8 g with 16 mL of *water* for 2 minutes, filter and dilute 5 mL of the filtrate to 15 mL with *water*. The solution complies with the *limit test for sulfates*, Appendix VII (600 ppm).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using three solutions in the mobile phase containing (1) 1.0% w/v of *dichlorophen impurity standard BPCRS*, (2) 1.0% w/v of the substance being examined and (3) 0.0010% w/v of *4-chlorophenol*.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a mixture of 25 volumes of *water* and 1 volume of *glacial acetic acid* and sufficient *methanol* to produce a chromatogram with solution (1) closely resembling the reference chromatogram supplied with the impurity standard (75 volumes of *methanol* is usually suitable) and (c) a detection wavelength of 280 nm. Record the chromatograms until all of the peaks named on the reference chromatogram have emerged.

In the chromatogram obtained with solution (2) the area of any peak corresponding to 4-chlorophenol is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%). The content of 4,4′-dichloro-2,2′-(2-hydroxy-4-chloro-*m*-xylene-*α*,*α*′-diyl)diphenol in the substance being examined does not exceed 8.0% w/w and the sum of the contents of any other impurities, excluding 4-chlorophenol, is not greater than 2.0% w/w calculated using the declared content of 4,4′-dichloro-2,2′-(2-hydroxy-4-chloro-*m*-xylene-*α*,*α*′-diyl)diphenol in *dichlorophen impurity standard BPCRS*.

Loss on drying

When dried to constant weight at 105°, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 0.5 g in 20 mL of *propan-2-ol* and carry out Method II for *non-aqueous titration*, Appendix VIII A, using 0.1M *tetrabutylammonium hydroxide VS* as titrant and determining the end point potentiometrically. Each mL of 0.1M *tetrabutylammonium hydroxide VS* is equivalent to 26.91 mg of $C_{13}H_{10}Cl_2O_2$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dichlorophen Tablets

General Notices

Action and use

Antihelminthic.

DEFINITION

Dichlorophen tablets contain Dichlorophen.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dichlorophen, $C_{13}H_{10}Cl_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.1 g of dichlorophen with 50 mL of 0.1M *sodium hydroxide* for 15 minutes, add sufficient 0.1M *sodium hydroxide* to produce 100 mL, centrifuge and dilute a suitable volume of the supernatant liquid with 0.1M *sodium hydroxide* to produce a solution containing 0.002% w/v of dichlorophen. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 350 nm exhibits two maxima, at 245 nm and 304 nm. The *absorbances* at the maxima are about 1.3 and about 0.54, respectively.

B. Shake a quantity of the powdered tablets containing 0.2 g of dichlorophen with a mixture of 5 mL of *water* and 5 mL of 5M *sodium hydroxide*, filter, cool in ice and add a solution prepared by mixing 1 mL of *sodium nitrite solution* with a cold solution containing 0.15 mL of *aniline* in a mixture of 4 mL of *water* and 1 mL of *hydrochloric acid*. A reddish brown precipitate is produced.

C. Fuse a quantity of the powdered tablets containing 0.5 g of dichlorophen with 2 g of *anhydrous sodium carbonate*, cool, extract the residue with *water* and filter. The filtrate yields reaction A characteristic *of chlorides*, Appendix VI.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.50 g of dichlorophen with 20 mL of *methanol* for 10 minutes, filter, add 7 mL of *water* and dilute to 50 mL with the mobile phase. Solution (2) contains 1.0% w/v of *dichlorophen impurity standard BPCRS* in the mobile phase. Solution (3) contains 0.0010% w/v of *4-chlorophenol* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a mixture of 1 volume of *glacial acetic acid* and 25 volumes of *water* and sufficient *methanol* to produce a chromatogram with solution (2) closely

www.webofpharma.com

https://thuocngocanh.com/

resembling the reference chromatogram supplied with the impurity standard (75 volumes of *methanol* is usually suitable) and (c) a detection wavelength of 280 nm. Record the chromatograms until all of the peaks named on the reference chromatogram have emerged.

In the chromatogram obtained with solution (1) the area of any peak corresponding to 4-chlorophenol is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%). Calculate the content of 4,4′-dichloro-2,2′-(2-hydroxy-4-chloro-*m*-xylene-α,α′-diyl)diphenol and the sum of the nominal contents of any other impurities, excluding 4-chlorophenol, with reference to dichlorophen using the declared content of 4,4′-dichloro-2,2′-(2-hydroxy-4-chloro-*m*-xylene-α,α′-diyl)diphenol in *dichlorophen impurity standard BPCRS*. The content of 4,4′-dichloro-2,2′-(2-hydroxy-4-chloro-*m*-xylene-α,α′-diyl)diphenol does not exceed 8.0% w/w and the sum of the nominal contents of any other impurities does not exceed 2% w/w.

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of dichlorophen with 50 mL of 0.1M *sodium hydroxide* for 15 minutes and add sufficient 0.1M *sodium hydroxide* to produce 100 mL. Centrifuge, dilute 10 mL of the clear supernatant liquid to 100 mL with 0.1M *sodium hydroxide*, dilute 20 mL of this solution to 100 mL with 0.1M *sodium hydroxide* and measure the *absorbance* of the resulting solution at the maximum at 304 nm, Appendix II B. Calculate the content of $C_{13}H_{10}Cl_2O_2$ taking 275 as the value of A(1%, 1 cm) at the maximum at 304 nm.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

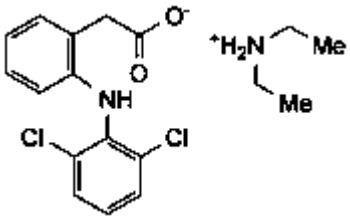
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diclofenac Diethylamine

General Notices



$C_{18}H_{22}Cl_2N_2O_2$ 369.29 *78213-16-8*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparation

Diclofenac Gel

DEFINITION

Diclofenac Diethylamine is diethylammonium 2-[(2,6-dichloroanilino)phenyl]acetate. It contains not less than 99.0% and not more than 101.0% of $C_{18}H_{22}Cl_2N_2O_2$, calculated with reference to the dried substance.

CHARACTERISTICS

A white to light beige, crystalline powder.

Sparingly soluble in *water* and in *acetone*; freely soluble in *ethanol (96%)* and in *methanol*; practically insoluble in 1M *sodium hydroxide*.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of diclofenac diethylamine *(RS 371)*.

TESTS

Acidity or alkalinity

pH of a 1% w/v solution in *ethanol (10%)*, 6.4 to 8.4, Appendix V L.

Clarity and colour of solution

www.webofpharma.com

https://thuocngocanh.com/

A 5% w/v solution in *methanol* is *clear*, Appendix IV A. The *absorbance* of the solution measured at 440 nm is not greater than 0.05, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) 0.1% w/v of the substance being examined.

(2) Dilute 1 volume of solution (1) to 50 volumes and dilute 1 volume of this solution to 10 volumes.

(3) 0.1% w/v of *diclofenac for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC-Pack Pro C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.6 times the retention time of diclofenac.

MOBILE PHASE

34 volumes of a mixture of equal volumes of a 0.05% w/v solution of *orthophosphoric acid* and a 0.08% w/v solution of *sodium dihydrogen orthophosphate*, previously adjusted to pH 2.5 with *orthophosphoric acid*, and 66 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to diclofenac (retention time about 25 minutes) are: impurity A, about 0.4 and impurity F, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity F and diclofenac is at least 4.0.

LIMITS

Identify any peaks due to impurities A and F in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity A by a correction factor of 0.7 and any peak corresponding to impurity F by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying

When dried at a pressure not exceeding 1 kPa for 24 hours, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A, Method II. Use 1 g.

ASSAY

Dissolve 0.3 g in 18 mL of *anhydrous acetic acid*. Carry out Method I for *non-aqueous titration*, Appendix VIII A, with *0.1M perchloric acid VS*, determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 36.93 mg of $C_{18}H_{22}Cl_2N_2O_2$.

STORAGE

Diclofenac Diethylamine should be kept in an airtight container and protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Diclofenac Sodium.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diclofenac Diethylamine Gel

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Diclofenac Diethylamine Gel contains Diclofenac Diethylamine in a suitable basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of diclofenac diethylamine, $C_{18}H_{22}Cl_2N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the gel containing 50 mg of Diclofenac Diethylamine, add 12.5 mL of *methanol* and mix with the aid of ultrasound for 10 minutes. Dilute to 25 mL with *methanol*, filter (a 0.45-µm PVDF is suitable) and use the filtrate.

(2) 0.2% w/v of *diclofenac diethylamine BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *octadecasilyl silica gel for HPTLC* (Merck silica gel HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry at 105° for 30 minutes. Spray with *ninhydrin solution* and heat at 105° for 45 minutes.

MOBILE PHASE

1 volume of *hydrochloric acid*, 1 volume of *water*, 6 volumes of *glacial acetic acid* and 11 volumes of *ethyl acetate*.

CONFIRMATION

The two principal spots in the chromatogram obtained with solution (1) correspond in position and colour to those in the chromatogram obtained with solution (2).

TESTS

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the gel containing 50 mg of Diclofenac Diethylamine with 50 mL of *acetone* for 10 minutes, filter and evaporate the filtrate to dryness under reduced pressure. Dissolve the residue in 10 mL of a mixture of 40 volumes of *water* and 60 volumes of *methanol*, dilute 1 volume of this solution to 5 volumes with the mobile phase and filter through a glass fibre filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.1% w/v of *diclofenac for system suitability EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC-Pack Pro C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 1.6 times the retention time of diclofenac.

MOBILE PHASE

34 volumes of a mixture of equal volumes of a 0.05% w/v solution of *orthophosphoric acid* and a 0.08% w/v solution of *sodium dihydrogen orthophosphate*, previously adjusted to pH 2.5 with *orthophosphoric acid*, and 66 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to diclofenac (retention time about 25 minutes) are: impurity A, about 0.4 and impurity F, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity F and diclofenac is at least 4.0.

LIMITS

Identify any peaks due to impurities A and F in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity A by a correction factor of 0.7 and any peak corresponding to impurity F by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the gel containing 50 mg of Diclofenac Diethylamine with 50 mL of *acetone* for 10 minutes, filter and evaporate the filtrate to dryness under reduced pressure. Dissolve the residue in 100 mL of a mixture of 40 volumes of *water* and 60 volumes of *methanol*, dilute 1 volume of this solution to 10 volumes with the mobile phase and filter through a glass fibre filter (Whatman GF/C is suitable).

(2) 0.05% w/v of *diclofenac sodium BPCRS* in *methanol*. Dilute 1 volume of the resulting solution to 10 volumes using the mobile phase.

(3) 0.1% w/v of *diclofenac sodium BPCRS* and 0.1% w/v of *diclofenac impurity A BPCRS* in *methanol*. Dilute 1 volume of the resulting solution to 10 volumes using the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (end-capped Zorbax C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of a mixture of equal volumes of a 0.1% w/v solution of *orthophosphoric acid* and a 0.16% w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 80 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention times are about 5 minutes for diclofenac and about 4 minutes for impurity A.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to diclofenac and impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{22}Cl_2N_2O_2$ in the gel using the declared content of $C_{14}H_{10}Cl_2NNaO_2$ in *diclofenac sodium BPCRS*. Each mg of $C_{14}H_{10}Cl_2NNaO_2$ is equivalent to 1.1609 mg of $C_{18}H_{22}Cl_2N_2O_2$.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diclofenac Gastro-resistant Tablets

General Notices

Diclofenac Tablets

Gastro-resistant Diclofenac Tablets

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Diclofenac Gastro-resistant Tablets contain Diclofenac Sodium. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diclofenac sodium, $C_{14}H_{10}Cl_2NNaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Remove the coating from 10 tablets and powder the cores. Add 0.5 mL of *glacial acetic acid* and 15 mL of *methanol* to a quantity of the powdered tablet cores containing 0.15 g of Diclofenac Sodium and mix with the aid of ultrasound. Shake gently for 1 minute, filter and collect the filtrate in 15 mL of *water*. Filter the precipitate under reduced pressure (a Whatman GF/C filter paper is suitable), wash with four 5-mL quantities of *water* and dry at 105° for 2 to 3 hours. The *infrared absorption spectrum* of the dried precipitate, Appendix II A, is concordant with the *reference spectrum* of diclofenac *(RS 096)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Diclofenac Sodium with 70 mL of the mobile phase for 30 minutes, add sufficient of the mobile phase to produce 100 mL, mix, centrifuge an aliquot and filter the supernatant liquid through a 0.45-µm filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of this solution to 5 volumes with the mobile phase.
(3) 0.0005% w/v of *diclofenac sodium BPCRS* and 0.0005% w/v of *diclofenac impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack-pro C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.5 times the retention time of diclofenac.

MOBILE PHASE

34 volumes of a mixture of equal volumes of a 0.1% w/v solution of *orthophosphoric acid* and a 0.16% w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 66 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to diclofenac (retention time about 25 minutes) are: impurity A, about 0.4 and impurity F, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to diclofenac and diclofenac impurity A is at least 6.5.

LIMITS

Identify the peak due to impurity A using the chromatogram obtained with solution (3) and multiply the area of this peak by a correction factor of 0.7. Identify the peak due to impurity F using the relative retention time and multiply the area of this peak by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 tablets with 700 mL of *methanol (50%)* for 30 minutes with the aid of ultrasound, add sufficient mobile phase to produce 1000 mL, centrifuge an aliquot and filter the supernatant liquid through a 0.45-µm filter. Dilute the filtrate with the mobile phase to produce a solution containing 0.005% w/v of Diclofenac Sodium.

(2) 0.005% w/v of *diclofenac sodium BPCRS* in the mobile phase.

(3) 0.0005% w/v of *diclofenac sodium BPCRS* and 0.0005% w/v of *diclofenac impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (end-capped Zorbax C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of a mixture of equal volumes of a 0.1% w/v solution of *orthophosphoric acid* and a 0.16% w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 80 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention times are about 5 minutes for diclofenac and about 4 minutes for diclofenac impurity A.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to diclofenac and diclofenac impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ in the tablets using the declared content of $C_{14}H_{10}Cl_2NNaO_2$ in *diclofenac sodium BPCRS*.

STORAGE

Diclofenac Gastro-resistant Tablets should be protected from moisture.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Diclofenac Sodium.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

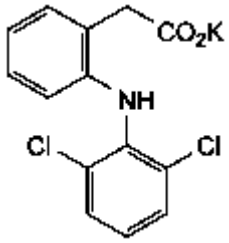
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diclofenac Potassium

General Notices

(Ph. Eur. monograph 1508)



$C_{14}H_{10}Cl_2KNO_2$ 334.2 *15307-81-0*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

Potassium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, slightly hygroscopic, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

www.webofpharma.com

https://thietbiuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *diclofenac potassium CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *diclofenac potassium CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *indometacin R* in reference solution (a) and dilute to 2 mL with the same solution.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *ethyl acetate R* (10:10:80 *V/V/V*).

Application 5 µL.

Development Over 1/2 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 10 mg in 10 mL of *ethanol (96 per cent) R*. To 1 mL of this solution add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of *potassium ferricyanide R* and a 9 g/L solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 mL of a 10 g/L solution of *hydrochloric acid R*. Allow to stand protected from light for 15 min. A blue colour develops and a precipitate is formed.

D. Suspend 0.5 g in 10 mL of *water R*. Stir and add *water R* until the substance is dissolved. Add 2 mL of *hydrochloric acid R1*, stir for 1 h and filter with the aid of vacuum. Neutralise with *sodium hydroxide solution R*. The solution gives reaction (b) of potassium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 440 nm is not greater than 0.05.

Dissolve 1.25 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *diclofenac for system suitability CRS* (containing impurities A and F) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 34 volumes of a solution containing 0.5 g/L of *phosphoric acid R* and 0.8 g/L of *sodium dihydrogen phosphate R*, previously adjusted to pH 2.5 with *phosphoric acid R*, and 66 volumes of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 1.6 times the retention time of diclofenac.

Identification of impurities Use the chromatogram supplied with *diclofenac for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and F.

Relative retention With reference to diclofenac (retention time = about 25 min): impurity A = about 0.4; impurity F = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurity F and diclofenac.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity F = 0.3;

— for each impurity, use the concentration of diclofenac potassium in reference solution (a).

Limits:

— *impurities A, F*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.250 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 33.42 mg of $C_{14}H_{10}Cl_2KNO_2$.

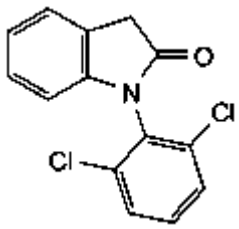
STORAGE

In an airtight container, protected from light.

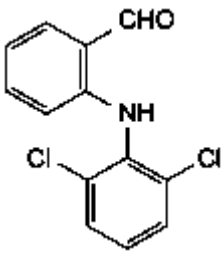
IMPURITIES

Specified impurities A, F.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E.



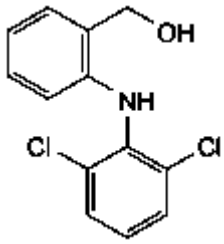
A. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one,



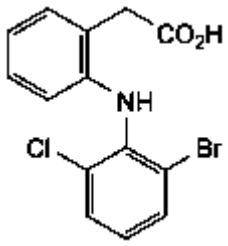
B. 2-[(2,6-dichlorophenyl)amino]benzaldehyde,

www.webofpharma.com

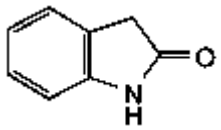
https://thuocngocanh.com/



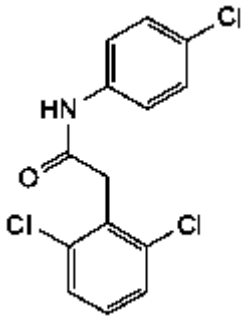
C. [2-[(2,6-dichlorophenyl)amino]phenyl]methanol,



D. [2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid,



E. 1,3-dihydro-2*H*-indol-2-one,



F. *N*-(4-chlorophenyl)-2-(2,6-dichlorophenyl)acetamide.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diclofenac Prolonged-release Capsules

General Notices

Prolonged-release Diclofenac Capsules

Diclofenac Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

DEFINITION

Diclofenac Prolonged-release Capsules contain Diclofenac Sodium. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Diclofenac Sodium. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of diclofenac sodium, $C_{14}H_{10}Cl_2NNaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Add 0.5 mL of *glacial acetic acid* and 15 mL of *methanol* to a quantity of the powdered capsule contents containing 0.15 g of Diclofenac Sodium and mix with the aid of ultrasound for 40 minutes. Shake gently for 1 minute, filter and collect the filtrate in 15 mL of *water*. Filter the precipitate (Whatman GF/C is suitable) under reduced pressure, wash with four 5-mL quantities of *water* and dry at 105° for 2 to 3 hours. The *infrared absorption spectrum* of the dried precipitate, Appendix II A, is concordant with the *reference spectrum* of diclofenac *(RS 096)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

To 30 volumes of *acetonitrile for chromatography* add 70 volumes of *water* (solvent A).

(1) Add 30 mL of solvent A to a quantity of the powdered contents of the capsules containing 0.1 g of Diclofenac Sodium and mix with the aid of ultrasound for 10 minutes with occasional shaking. Cool, add sufficient solvent A to produce 50 mL and filter (Whatman GF/C is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A and dilute 1 volume of this solution to 5 volumes with solvent A.

(3) 0.0005% w/v of *diclofenac sodium BPCRS* and 0.0005% w/v of *diclofenac impurity A BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *base-deactivated, end-capped octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP Select B or equivalent is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

A mixture of 5 volumes of *tetrahydrofuran*, 30 volumes of *acetonitrile* and 65 volumes of 0.05M *ammonium dihydrogen orthophosphate*, previously adjusted to pH 5.0 using 18M *ammonia*.

When the chromatograms are recorded under the prescribed conditions, the retention times are about 18 minutes for diclofenac and about 26 minutes for diclofenac impurity A. Continue the chromatography for 5 times the retention time of diclofenac.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to diclofenac and diclofenac impurity A is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust the pH to 6.8 with 1M *sodium hydroxide* (solution A). To a quantity of the mixed contents of 20 capsules containing 100 mg of Diclofenac Sodium add 10 mL of *ethanol (96%)* and mix with the aid of ultrasound for 20 minutes or until completely dispersed. Add 150 mL of solution A and mix with the aid of ultrasound for a further 20 minutes or until completely dispersed. Cool to room temperature, dilute to 250 mL with solution A and shake thoroughly. Filter the resulting solution and dilute 5 mL to 100 mL with solution A. Prepare a reference standard in the following manner. Dissolve 50 mg of *diclofenac sodium BPCRS* in 10 mL of *ethanol (96%)* with the aid of ultrasound for 5 minutes. Add 150 mL of solution A and mix with the aid of ultrasound for a further 5 minutes. Cool to room temperature, dilute to 250 mL with solution A and shake thoroughly. Dilute 5 mL of the resulting solution to 50 mL with solution A. Measure the *absorbance*, Appendix II B, of the solutions at 275 nm using in the reference cell a 0.4% v/v solution of *ethanol (96%)* in solution A.

www.webofpharma.com

https://thuathuocngocanh.com/

Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ in the capsules using the *absorbances* at the maximum at 275 nm and the declared content of $C_{14}H_{10}Cl_2NNaO_2$ in *diclofenac sodium BPCRS*.

STORAGE

Diclofenac Prolonged-release Capsules should be protected from moisture.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Diclofenac Sodium.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diclofenac Prolonged-release Tablets

General Notices

Prolonged-release Diclofenac Tablets

Diclofenac Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Diclofenac Prolonged-release Tablets contain Diclofenac Sodium. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of diclofenac sodium. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diclofenac sodium, $C_{14}H_{10}Cl_2NNaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Remove the coating from 10 tablets and powder the cores. To a quantity of the powdered tablet cores containing 0.15 g of Diclofenac Sodium, add 0.5 mL of *glacial acetic acid* and 15 mL of *methanol* and mix with the aid of ultrasound. Shake gently for 1 minute, filter and collect the filtrate in 15 mL of *water*. Filter the precipitate under reduced pressure (Whatman GF/C filter paper is suitable), wash with four 5-mL quantities of *water* and dry at 105° for 2 to 3 hours. The *infrared absorption spectrum* of the dried precipitate, Appendix II A, is concordant with the *reference spectrum* of diclofenac *(RS 096)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of the powdered tablets containing 50 mg of Diclofenac Sodium with 70 mL of the mobile phase for 30 minutes, add sufficient of the mobile phase to produce 100 mL, mix, centrifuge an aliquot and filter the supernatant liquid through a 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of this solution to 5 volumes with the mobile phase.

(3) 0.0005% w/v of *diclofenac sodium BPCRS* and 0.0005% w/v of *diclofenac impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack-pro C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.5 times the retention time of diclofenac.

MOBILE PHASE

34 volumes of a mixture of equal volumes of a 0.1% w/v solution of *orthophosphoric acid* and a 0.16% w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 66 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to diclofenac (retention time about 25 minutes) are: impurity A, about 0.4 and impurity F, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to diclofenac and diclofenac impurity A is at least 6.5.

LIMITS

Identify the peak due to impurity A using the chromatogram obtained with solution (3) and multiply the area of the peak by a correction factor of 0.7. Identify the peak due to impurity F using the relative retention time and multiply the area of the peak by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) To a quantity of the powdered tablets containing 0.5 g of Diclofenac Sodium add 800 mL of *methanol* and mix with the aid of ultrasound. Dilute the resulting solution with the mobile phase to produce a solution containing 0.005% w/v of Diclofenac Sodium.

(2) 0.005% w/v of *diclofenac sodium BPCRS* in the mobile phase.

(3) 0.0005% w/v of *diclofenac sodium BPCRS* and 0.0005% w/v of *diclofenac impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Zorbax C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of a mixture of equal volumes of a 0.1% w/v solution of *phosphoric acid* and a 0.16% w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 80 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention times are about 5 minutes for diclofenac and about 4 minutes for diclofenac impurity A.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to diclofenac and diclofenac impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ in the tablets using the declared content of $C_{14}H_{10}Cl_2NNaO_2$ in *diclofenac sodium BPCRS*.

STORAGE

Diclofenac Prolonged-release Tablets should be protected from moisture.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Diclofenac Sodium.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuathuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

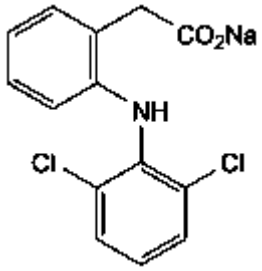
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diclofenac Sodium

General Notices

(Ph. Eur. monograph 1002)



$C_{14}H_{10}Cl_2NNaO_2$ 318.1 *15307-79-6*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparations

Diclofenac Prolonged-release Capsules

Diclofenac Gastro-resistant Tablets

Diclofenac Prolonged-release Tablets

Ph Eur

DEFINITION

Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish, slightly hygroscopic, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.

mp

About 280 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *diclofenac sodium CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 25 mg of *diclofenac sodium CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *indometacin R* in reference solution (a) and dilute to 2 mL with reference solution (a).

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *ethyl acetate R* (10:10:80 *V/V/V*).

Application 5 µL.

Development Over 1/2 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 10 mg in 10 mL of *ethanol (96 per cent) R*. To 1 mL of this solution add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of *potassium ferricyanide R* and a 9 g/L solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 mL of a 10 g/L solution of *hydrochloric acid R*. Allow to stand, protected from light, for 15 min. A blue colour develops and a precipitate is formed.

D. Dissolve 60 mg in 0.5 mL of *methanol R* and add 0.5 mL of *water R*. The solution gives reaction (b) of sodium (2.3.1).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 440 nm is not greater than 0.05.

Dissolve 1.25 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *diclofenac for system suitability CRS* (containing impurities A and F) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 34 volumes of a solution containing 0.5 g/L of *phosphoric acid R* and 0.8 g/L of *sodium dihydrogen phosphate R*, previously adjusted to pH 2.5 with *phosphoric acid R*, and 66 volumes of *methanol R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 1.6 times the retention time of diclofenac.

Identification of impurities Use the chromatogram supplied with *diclofenac for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and F.

Relative retention With reference to diclofenac (retention time = about 25 min): impurity A = about 0.4; impurity F = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurity F and diclofenac.

Calculation of percentage contents:

www.webofpharma.com

https://thietbiuocngocanh.com/

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity F = 0.3;

— for each impurity, use the concentration of diclofenac sodium in reference solution (a).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *impurity F*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.250 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 31.81 mg of $C_{14}H_{10}Cl_2NNaO_2$.

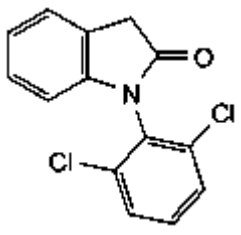
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, F.*

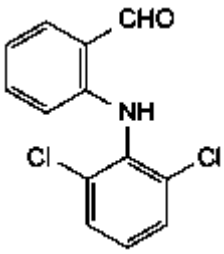
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E.*



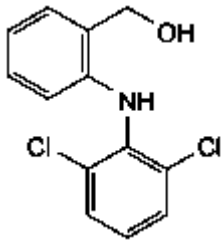
www.webofpharma.com

https://thuocngocanh.com/

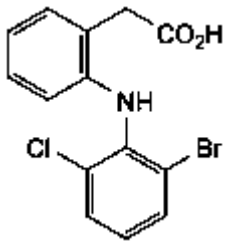
A. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one,



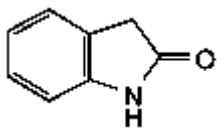
B. 2-[(2,6-dichlorophenyl)amino]benzaldehyde,



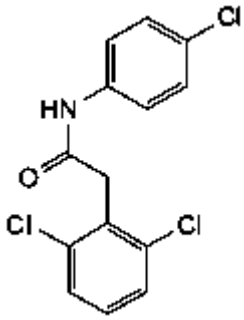
C. [2-[(2,6-dichlorophenyl)amino]phenyl]methanol,



D. [2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid,



E. 1,3-dihydro-2*H*-indol-2-one,



F. *N*-(4-chlorophenyl)-2-(2,6-dichlorophenyl)acetamide.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

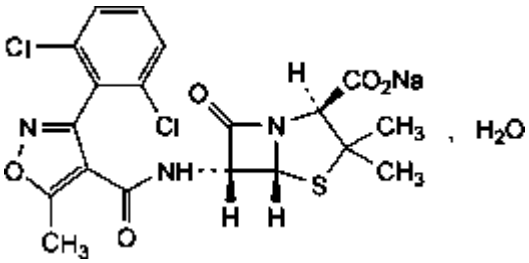
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dicloxacillin Sodium

General Notices

(Ph. Eur. monograph 0663)



$C_{19}H_{16}Cl_2N_3NaO_5S,H_2O$ 510.3 *13412-64-1*

Action and use

Penicillin antibacterial.

Ph Eur

DEFINITION

Sodium (2*S*,5*R*,6*R*)-6-[[[3-(2,6-dichlorophenyl)-5-methyl-1,2-oxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *dicloxacillin sodium CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *water R*.

Reference solution (a) Dissolve 25 mg of *dicloxacillin sodium CRS* in 5 mL of *water R*.

Reference solution (b) Dissolve 25 mg of *cloxacillin sodium CRS*, 25 mg of *dicloxacillin sodium CRS* and 25 mg of *flucloxacillin sodium CRS* in 5 mL of *water R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and about 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the solution is slightly greenish-yellow. Place the test-tube in a water-bath for 1 min; a yellow colour develops.

D. It gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is clear (2.2.1) and its absorbance (2.2.25) at 430 nm is not greater than 0.04.

pH (2.2.3)

5.0 to 7.0 for solution S.

Specific optical rotation (2.2.7)

+ 128 to + 143 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *dicloxacillin sodium CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of test solution (b) to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *flucloxacillin sodium CRS* and 5 mg of *dicloxacillin sodium CRS* in the mobile phase, then dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 25 volumes of *acetonitrile R* and 75 volumes of a 2.7 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 5.0 with *dilute sodium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL of test solution (a) and reference solutions (b) and (c).

Run time 5 times the retention time of dicloxacillin.

Retention time Dicloxacillin = about 10 min.

System suitability Reference solution (c):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 2.5 between the peaks due to flucloxacillin (1st peak) and dicloxacillin (2nd peak).

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (5 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

_N,N_-Dimethylaniline (*2.4.26, Method B*)

Maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.8 per cent *m/m*.

Water (*2.5.12*)

3.0 per cent to 4.5 per cent, determined on 0.300 g.

Pyrogens (*2.6.8*)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of pyrogens, it complies with the test for pyrogens. Inject per kilogram of the rabbit's mass 1 mL of a solution in *water for injections R* containing 20 mg of the substance to be examined per millilitre.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

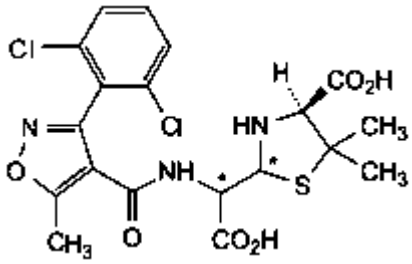
STORAGE

In an airtight container, at a temperature not exceeding 25 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

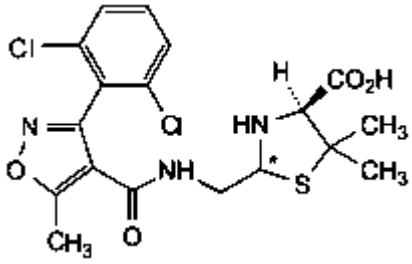
IMPURITIES

www.webofpharma.com

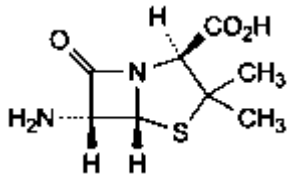
https://thuocngocanh.com/



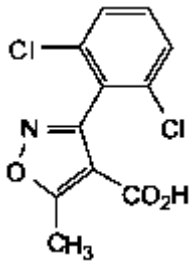
A. (4*S*)-2-[carboxy[[[3-(2,6-dichlorophenyl)-5-methyl-1,2-oxazol-4-yl]carbonyl]amino]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of dicloxacillin),



B. (2*RS*,4*S*)-2-[[[[3-(2,6-dichlorophenyl)-5-methyl-1,2-oxazol-4-yl]carbonyl]amino]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penilloic acids of dicloxacillin),



C. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



D. 3-(2,6-dichlorophenyl)-5-methyl-1,2-oxazole-4-carboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

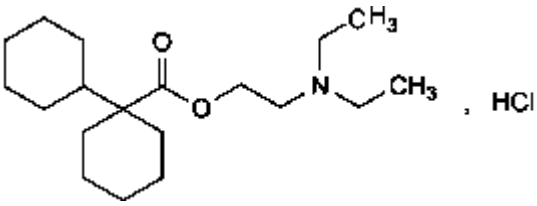
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dicycloverine Hydrochloride

General Notices

(Ph. Eur. monograph 1197)



$C_{19}H_{36}ClNO_2$ 346.0

Action and use

Anticholinergic.

Preparations

Dicycloverine Oral Solution

Dicycloverine Tablets

Ph Eur

DEFINITION

2-(Diethylamino)ethyl 1,1′-(bicyclohexane)-1-carboxylate hydrochloride.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *dicycloverine hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 50 mL with the same solvent.

Reference solution Dissolve 10 mg of *dicycloverine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*

Mobile phase *concentrated ammonia R*, *ethyl acetate R*, *water R*, *propanol R* (5:10:10:75 *V/V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Spray with *dilute potassium iodobismuthate solution R*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 3 mL of a 1.0 g/L solution of *sodium laurilsulfate R* add 5 mL of *methylene chloride R* and 0.05 mL of a 2.5 g/L solution of *methylene blue R*, mix gently and allow to separate; the lower layer is blue. Add 2 mL of a 20 g/L solution of the substance to be examined, mix gently and allow to separate; the upper layer is blue and the lower layer is colourless.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

5.0 to 5.5.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *dicycloverine for system suitability CRS* (containing impurity B) in 1 mL of the mobile phase.

Reference solution (c) Dissolve 7.5 mg of *dicycloverine impurity A CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase Mix 15 volumes of a 4.62 g/L solution of *ammonium acetate R* previously adjusted to pH 8.0 with *2 M sodium hydroxide R* and 85 volumes of *methanol R2*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL.

Run time 1.5 times the retention time of dicycloverine.

Identification of impurities Use the chromatogram supplied with *dicycloverine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to dicycloverine (retention time = about 22 min): impurity A = about 0.5; impurity B = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity B and dicycloverine.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity B by 0.4;

— for impurity A, use the concentration of impurity A in reference solution (c);

— for impurities other than A, use the concentration of dicycloverine hydrochloride in reference solution (a).

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity B*: maximum 0.5 per cent;

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.7 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

Maximum 1.0 per cent, determined on 1.00 g by direct introduction of the sample.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

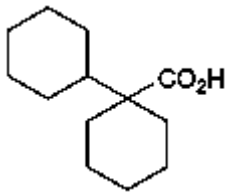
ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

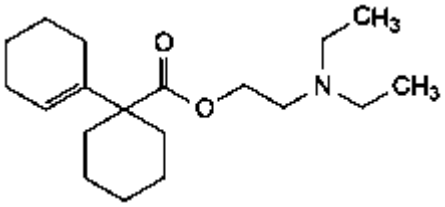
1 mL of *0.1 M sodium hydroxide* is equivalent to 34.60 mg of $C_{19}H_{36}ClNO_2$.

IMPURITIES

Specified impurities *A, B.*



A. 1,1′-bi(cyclohexane)-1-carboxylic acid,



B. 2-(diethylamino)ethyl 1,1′-bi(cyclohexan)-1′-ene-1-carboxylate.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dicycloverine Oral Solution

General Notices

Action and use

Anticholinergic.

DEFINITION

Dicycloverine Oral Solution is a solution of Dicycloverine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of dicycloverine hydrochloride, $C_{19}H_{35}NO_2$,HCl

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a volume containing 0.1 g of dicycloverine hydrochloride add 10 mL of *water* and 1 mL of *hydrochloric acid*, shake with 30 mL of *ether* and allow to separate. Extract the aqueous layer with 30 mL of *chloroform*, wash the extract with two 10 mL quantities of *water* and filter the chloroform solution through *anhydrous sodium sulfate*. Evaporate the filtrate to dryness, recrystallise the residue from hot *acetone* and dry the precipitate at 105° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dicycloverine hydrochloride (*RS 098*).

B. Acidify the oral solution with 2M *nitric acid* and add *silver nitrate solution*. A white precipitate is produced.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 10 mL of *water* and 1 mL of *hydrochloric acid* to a volume containing 0.1 g of dicycloverine hydrochloride, shake with 30 mL of *ether* and allow to separate. Extract the aqueous layer with 30 mL of *dichloromethane*, wash the extract with two 10 mL quantities of *water*, shake with *anhydrous sodium sulfate*, filter (Whatman 1PS paper is suitable), evaporate the filtrate to dryness and dissolve the residue in 4 mL of *dichloromethane*.

(2) Dilute 1 volume of solution (1) to 500 volumes with *dichloromethane*.

(3) 0.1% w/v of each of *dicycloverine hydrochloride BPCRS* and *tropicamide BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel. G*

(b) Use the mobile phase as described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in a current of warm air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

5 volumes of 13.5M *ammonia*, 10 volumes of *ethyl acetate*, 10 volumes of *water* and 75 volumes of *propan-1-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%).

Disregard any spot remaining on the line of application.

ASSAY

To a weighed quantity containing 5 mg of dicycloverine hydrochloride add 5 mL of *sulfuric acid (10%)* and 2 mL of 0.02M *potassium permanganate*, mix, allow to stand, add 20 mL of *water* and 20 mL of *chloroform* to the decolourised solution and titrate with 0.001M *sodium dodecyl sulfate VS* using 1 mL of *dimethyl yellow solution* as indicator. Each mL of 0.001M *sodium dodecyl sulfate VS* is equivalent to 0.3460 mg of $C_{19}H_{35}NO_2$,HCl. Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{19}H_{35}NO_2$,HCl, weight in volume.

STORAGE

Dicycloverine Oral Solution should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dicycloverine Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Dicycloverine Tablets contain Dicycloverine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dicycloverine hydrochloride, $C_{19}H_{35}NO_2$,HCl

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 0.2 g of Dicycloverine Hydrochloride with 20 mL of *chloroform*, filter, evaporate the filtrate to dryness, recrystallise the residue from *acetone* and dry at 105° for 4 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dicycloverine hydrochloride *(RS 098)*.

B. Shake a quantity of the powdered tablets containing 10 mg of Dicycloverine Hydrochloride with 5 mL of *water* and 0.2 mL of 2M *nitric acid*, filter and add 0.5 mL of *silver nitrate solution* to the filtrate. A white precipitate is produced.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.2 g of Dicycloverine Hydrochloride with 8 mL of *water* and 2 mL of 13.5M *ammonia*, extract with two 20-mL quantities of *dichloromethane*, shake with *anhydrous sodium sulfate*, filter (Whatman 1PS paper is suitable), evaporate the filtrate to dryness and dissolve the residue in 4 mL of *dichloromethane*.

(2) Dilute 1 volume of solution (1) to 500 volumes with *dichloromethane*.

(3) 0.1% w/v of each of *dicycloverine hydrochloride BPCRS* and *tropicamide BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel G plate*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

www.webofpharma.com

https://thuathuocngocanh.com/

(e) After removal of the plate, dry in a current of warm air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

5 volumes of 13.5M *ammonia*, 10 volumes of *ethyl acetate*, 10 volumes of *water* and 75 volumes of *propan-1-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1), any *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.2%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 30 mg of Dicycloverine Hydrochloride add 20 mL of *water* and shake. Add 10 mL of 1M *sulfuric acid*, 1 mL of *dimethyl yellow solution* and 40 mL of *chloroform*, shake and titrate with 0.004M *sodium dodecyl sulfate VS*, shaking vigorously and allowing the layers to separate after each addition, until a permanent orange–pink colour is produced in the chloroform layer. Each mL of 0.004M *sodium dodecyl sulfate VS* is equivalent to 1.384 mg of $C_{19}H_{35}NO_2$,HCl.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

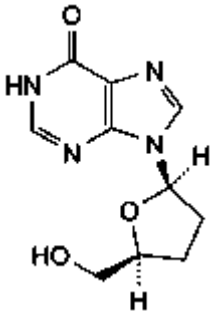
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Didanosine

General Notices

(Ph. Eur. monograph 2200)



$C_{10}H_{12}N_4O_3$ 236.2 *69655-05-6*

Action and use

Nucleoside reverse transcriptase inhibitor; antiviral (HIV).

Ph Eur

DEFINITION

9-(2,3-Dideoxy-β-D-*glycero*-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one (2′,3′-dideoxyinosine).

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in dimethyl sulfoxide, slightly soluble in methanol and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *didanosine CRS*.

B. Specific optical rotation (2.2.7): -28.2 to -24.2 (anhydrous substance).

Dissolve 0.100 g in *water R* and dilute to 10.0 mL with the same solvent.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture Mix 8 volumes of mobile phase B and 92 volumes of mobile phase A.

Test solution Dissolve 25.0 mg of the substance to be examined in 50.0 mL of the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5.0 mg of *didanosine impurity A CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *didanosine for system suitability CRS* (containing impurities A to F) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of *didanosine impurity G CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 8 volumes of *methanol R* and 92 volumes of a 3.86 g/L solution of *ammonium acetate R* adjusted to pH 8.0 with *concentrated ammonia R*;

— *mobile phase B*: mix 30 volumes of *methanol R* and 70 volumes of a 3.86 g/L solution of *ammonium acetate R* adjusted to pH 8.0 with *concentrated ammonia R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	100	0
18 - 25	100 → 0	0 → 100
25 - 45	0	100

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
45 - 50	0 → 100	100 → 0
50 - 60	100	0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *didanosine for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A to F and use the chromatogram obtained with reference solution (d) to identify the peak due to impurity G.

Relative retention With reference to didanosine (retention time = about 13-15 min): impurity A = about 0.3; impurity B = about 0.4; impurity C = about 0.44; impurity D = about 0.48; impurity E = about 0.5; impurity F = about 0.8; impurity G = about 1.6.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to impurity C and impurity D.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities B, C, D, E, F, G*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 2.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

www.webofpharma.com

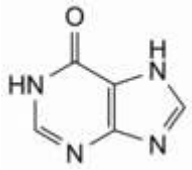
https://thuocngocanh.com/

1 mL of *0.1 M perchloric acid* is equivalent to 23.62 mg of $C_{10}H_{12}N_4O_3$.

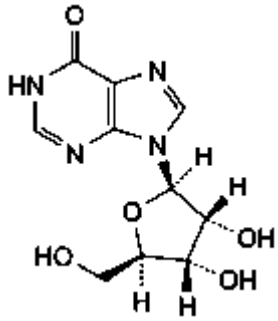
IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

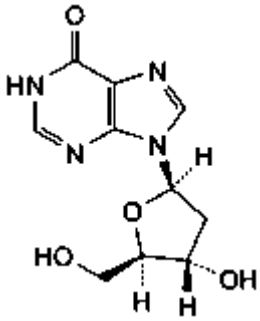
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H, I.*



A. 1,7-dihydro-6*H*-purin-6-one (hypoxanthine),



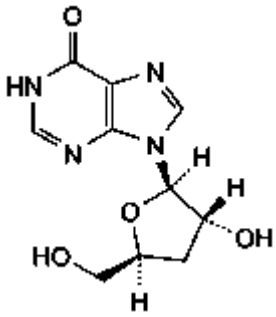
B. 9-β-D-ribofuranosyl-1,9-dihydro-6*H*-purin-6-one (inosine),



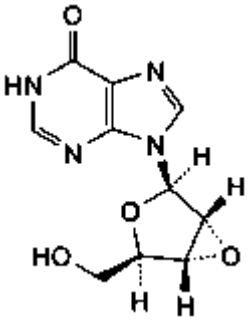
C. 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one (2′-deoxyinosine),

www.webofpharma.com

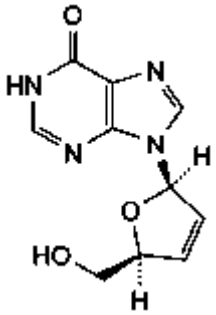
https://thuocngocanh.com/



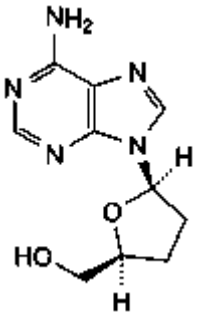
D. 9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one (3′-deoxyinosine),



E. 9-(2,3-anhydro-β-D-ribofuranosyl)-1,9-dihydro-6*H*-purin-6-one (2′,3′-anhydroinosine),



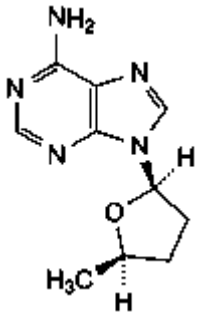
F. 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-1,9-dihydro-6*H*-purin-6-one (2′,3′-dideoxy-2′,3′-didehydroinosine),



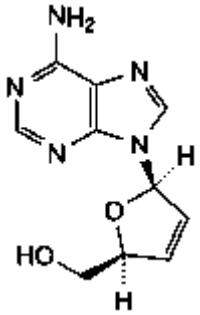
G. 9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-9*H*-purin-6-amine (2′,3′-dideoxyadenosine),

www.webofpharma.com

https://thuocngocanh.com/



H. 9-(2,3,5-trideoxy-β-D-*glycero*-pentofuranosyl)-9*H*-purin-6-amine (2′,3′,5′-trideoxyadenosine),



I. 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-9*H*-purin-6-amine (2′,3′-dideoxy-2′,3′-didehydroadenosine).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

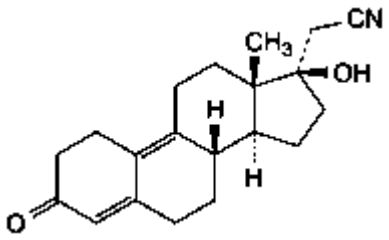
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dienogest

General Notices

(Ph. Eur. monograph 2732)



$C_{20}H_{25}NO_2$ 311.4 *65928-58-7*

Action and use

Progestogen.

Ph Eur

DEFINITION

(17-Hydroxy-3-oxoestra-4,9-dien-17α-yl)acetonitrile.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White, almost white or slightly yellow, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in methanol.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *dienogest CRS*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Specific optical rotation (2.2.7)

-352 to -344 (dried substance).

Dissolve 0.125 g in *methanol R2* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture *acetonitrile R1*, *water for chromatography R* (40:60 *V/V*).

Test solution (a) Dissolve 20 mg of the substance to be examined in 8 mL of *acetonitrile R1* and dilute to 20.0 mL with *water R*.

Test solution (b) Dissolve 30.0 mg of the substance to be examined in 40 mL of *acetonitrile R1* and dilute to 100.0 mL with *water R*. Dilute 5.0 mL of the solution to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2.5 mg of *dienogest for system suitability CRS* (containing impurity F) in 2 mL of *acetonitrile R1* and dilute to 5.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 30.0 mg of *dienogest CRS* in 40 mL of *acetonitrile R1* and dilute to 100.0 mL with *water R*. Dilute 5.0 mL of the solution to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, *water for chromatography R* (10:90 *V/V*);

— *mobile phase B*: *water for chromatography R*, *acetonitrile R1* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	90	10
3 - 53	90 → 10	10 → 90

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 15 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *dienogest for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity F.

Relative retention With reference to dienogest (retention time = about 19 min): impurity F = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to dienogest and impurity F.

Calculation of percentage contents:

— for each impurity, use the concentration of dienogest in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	75	25
3 - 14	75 → 25	25 → 75

Detection Spectrophotometer at 215 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection Test solution (b) and reference solution (c).

Retention time Dienogest = about 9 min.

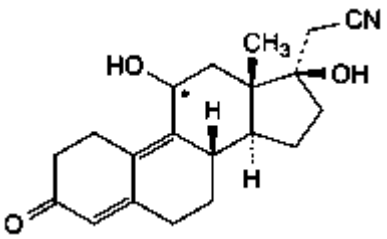
Calculate the percentage content of $C_{20}H_{25}NO_2$ taking into account the assigned content of *dienogest CRS*.

STORAGE

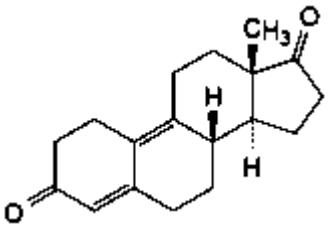
Protected from light.

IMPURITIES

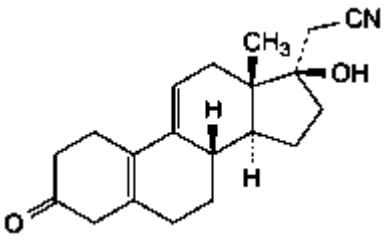
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I, J, K, L, M.



A. (11,17-dihydroxy-3-oxoestra-4,9-dien-17α-yl)acetonitrile,



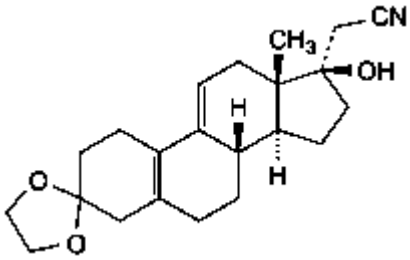
B. estra-4,9-diene-3,17-dione,



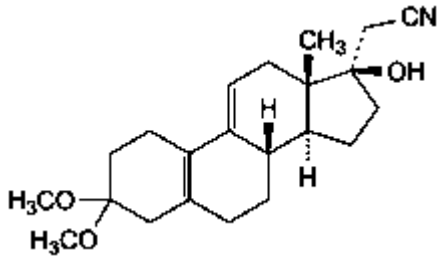
C. [17-hydroxy-3-oxoestra-5(10),9(11)-dien-17α-yl]acetonitrile,

www.webofpharma.com

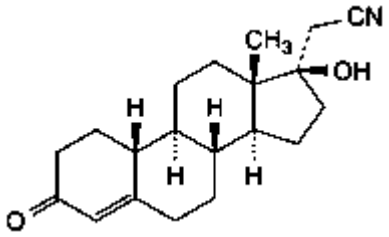
https://thuocngocanh.com/



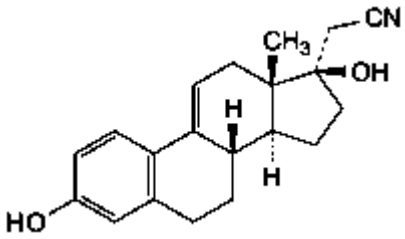
D. [17′-hydroxyspiro[1,3-dioxolan-2,3′-estra-5′(10′),9′(11′)-dien]-17′α-yl]acetonitrile,



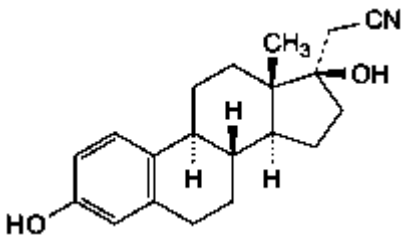
E. [17-hydroxy-3,3-dimethoxyestra-5(10),9(11)-dien-17α-yl]acetonitrile,



F. (17-hydroxy-3-oxoestr-4-en-17α-yl)acetonitrile,



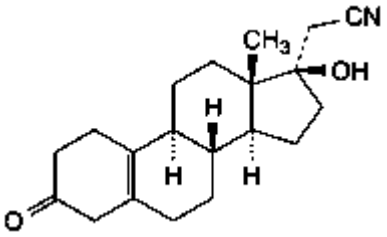
G. [3,17-dihydroxyestra-1,3,5(10),9(11)-tetraen-17α-yl]acetonitrile,



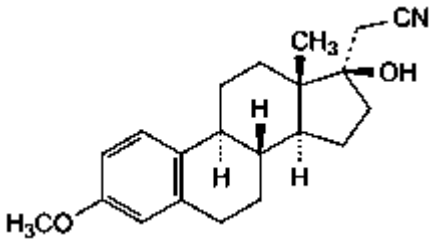
H. [3,17-dihydroxyestra-1,3,5(10)-trien-17α-yl]acetonitrile,

www.webofpharma.com

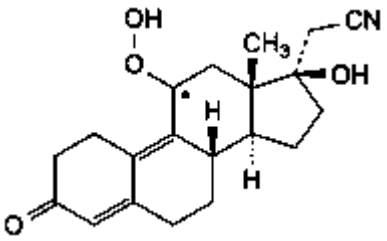
https://thuocngocanh.com/



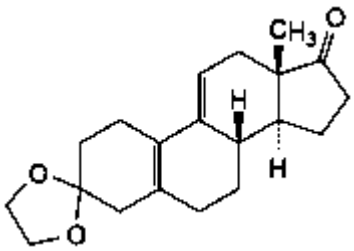
I. [17-hydroxy-3-oxoestr-5(10)-en-17α-yl]acetonitrile,



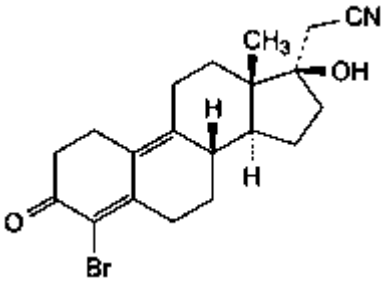
J. [17-hydroxy-3-methoxyestra-1,3,5(10)-trien-17α-yl]acetonitrile,



K. (11-hydroperoxy-17-hydroxy-3-oxoestra-4,9-dien-17α-yl)acetonitrile,



L. spiro[1,3-dioxolan-2,3′-estra-5′(10′),9′(11′)-dien]-17′-one,



M. (4-bromo-17-hydroxy-3-oxoestra-4,9-dien-17α-yl)acetonitrile.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

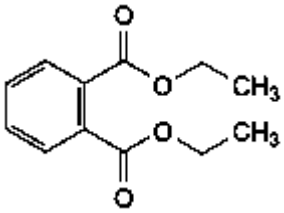
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diethyl Phthalate

General Notices

(Ph. Eur. monograph 0897)



$C_{12}H_{14}O_4$ 222.2 *84-66-2*

Action and use

Excipient.

Ph Eur

DEFINITION

Diethyl benzene-1,2-dicarboxylate.

Content

99.0 per cent *m/m* to 101.0 per cent *m/m*.

CHARACTERS

Appearance

Clear, colourless or very slightly yellow, oily liquid.

Solubility

Practically insoluble in water, miscible with ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, D, E.

www.webofpharma.com

https://thuocngocanh.com/

A. Relative density (2.2.5): 1.117 to 1.121.

B. Refractive index (2.2.6): 1.500 to 1.505.

C. Infrared absorption spectrophotometry (2.2.24).

Preparation Thin films.

Comparison *diethyl phthalate CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *ether R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 50 mg of *diethyl phthalate CRS* in *ether R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *heptane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

E. To about 0.1 mL add 0.25 mL of *sulfuric acid R* and 50 mg of *resorcinol R*. Heat on a water-bath for 5 min. Allow to cool. Add 10 mL of *water R* and 1 mL of *strong sodium hydroxide solution R*. The solution becomes yellow or brownish-yellow and shows green fluorescence.

TESTS

Appearance

The substance to be examined is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Acidity

Dissolve 20.0 g in 50 mL of *ethanol (96 per cent) R* previously neutralised to *phenolphthalein solution R1*. Add 0.2 mL of *phenolphthalein solution R1*. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances

Gas chromatography (2.2.28).

Internal standard solution Dissolve 60 mg of *naphthalene R* in *methylene chloride R* and dilute to 20 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20.0 mL with the same solvent.

Test solution (b) Dissolve 1.0 g of the substance to be examined in *methylene chloride R*, add 2.0 mL of the internal standard solution and dilute to 20.0 mL with *methylene chloride R*.

Reference solution To 1.0 mL of test solution (a) add 10.0 mL of the internal standard solution and dilute to 100.0 mL with *methylene chloride R*.

Column:

— *material*: glass;

— *size*: *l* = 2 m, Ø = 2 mm;

— *stationary phase*: *silanised diatomaceous earth for gas chromatography R* (150-180 µm) impregnated with 3 per cent *m/m* of *phenyl(50)methyl(50)polysiloxane R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 150 °C;

— *injection port and detector*: 225 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time 3 times the retention time of diethyl phthalate.

Elution order Naphthalene, diethyl phtalate.

System suitability:

— *resolution*: minimum 10 between the peaks due to naphthalene and diethyl phthalate in the chromatogram obtained with the reference solution;

— in the chromatogram obtained with test solution (a), there is no peak with the same retention time as the internal standard.

Limit:

— *total*: calculate the ratio (*R*) of the area of the peak due to diethyl phthalate to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with test solution (b), calculate the ratio of the sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than *R* (1.0 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Water (*2.5.12*)

Maximum 0.2 per cent, determined on 10.0 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Introduce 0.750 g into a 250 mL borosilicate glass flask. Add 25.0 mL of *0.5 M alcoholic potassium hydroxide* and a few glass beads. Boil in a water-bath under a reflux condenser for 1 h. Add 1 mL of *phenolphthalein solution R1* and titrate immediately with *0.5 M hydrochloric acid*. Carry out a blank titration. Calculate the volume of *0.5 M alcoholic potassium hydroxide* used in the saponification.

1 mL of *0.5 M alcoholic potassium hydroxide* is equivalent to 55.56 mg of $C_{12}H_{14}O_4$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

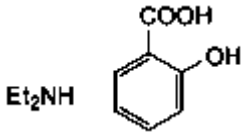
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diethylamine Salicylate

General Notices



$C_{11}H_{17}NO_3$ 211.3 *4419-92-5*

Action and use

Counter-irritant.

Preparation

Diethylamine Salicylate Cream

DEFINITION

Diethylamine Salicylate contains not less than 99.0% and not more than 101.0% of $C_{11}H_{17}NO_3$.

CHARACTERISTICS

White or almost white crystals.

Very soluble in *water*; freely soluble in *ethanol (96%)*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of diethylamine salicylate *(RS 099)*.

B. To 0.2 g add 5 mL of 1M *sodium hydroxide*, heat to boiling point, cool and acidify with *2M hydrochloric acid*; a white precipitate is produced. The *melting point* of the precipitate, after recrystallisation from *water* and drying at 105°, is about 160°, Appendix V A.

TESTS

Acidity

Dissolve 2 g in 25 mL of *water* and titrate with *0.1M sodium hydroxide VS* using *phenol red solution* as indicator. Not more than 0.2 mL of *0.1M sodium hydroxide VS* is required to change the colour of the solution.

Clarity and colour of solution

www.webofpharma.com

https://thuocngocanh.com/

A 50% w/v solution is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* BY_5, Appendix IV B, Method II.

Melting point

100° to 102°, Appendix V A.

Sulfate

0.6 g complies with the *limit test for sulfates*, Appendix VII (250 ppm).

Loss on drying

When dried at 60° for 3 hours, loses not more than 0.1% of its weight. Use 1 g.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.4 g and *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 21.13 mg of $C_{11}H_{17}NO_3$.

STORAGE

Diethylamine Salicylate should be protected from light. It should not be allowed to come into contact with iron or iron salts.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diethylamine Salicylate Cream

General Notices

DEFINITION

Diethylamine Salicylate Cream is a dispersion of Diethylamine Salicylate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of diethylamine salicylate, $C_{11}H_{17}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To 5 g add 50 mL of 2M *sodium hydroxide*, shake well and filter. Acidify 30 mL of the filtrate with 2M *hydrochloric acid*, cool and allow to stand. The *infrared absorption spectrum* of the resulting precipitate, after recrystallisation from *water* and drying at 105°, Appendix II A, is concordant with the *reference spectrum* of salicylic acid *(RS 316)*.

B. To 5 mL of the filtrate obtained in test A, add 10 mL of *water* and 0.05 mL of *iron(III) chloride solution R1*. A deep violet colour is produced.

C. Mix 3 g with 25 mL of *chloroform* and shake with 20 mL of 0.1M *hydrochloric acid*. To the acidic layer add 10 mL of 2M *sodium hydroxide* and boil. Diethylamine vapour is evolved, which turns moist *red litmus paper* blue.

ASSAY

To a quantity containing 50 mg of diethylamine salicylate add 30 mL of 0.5M *sodium hydroxide* and 15 mL of *ethanol (96%)*, mix, heat under a reflux condenser for 30 minutes and cool. To the resulting mixture add 20 mL of 1M *hydrochloric acid*, mix, dilute to 250 mL with *water* and filter. Shake 15 mL of the filtrate with 25 mL of *chloroform* for 2 minutes. To 5 mL of the chloroform layer add 10 mL of *iron(III) nitrate solution* and shake for 5 minutes. Centrifuge the aqueous layer and measure the *absorbance* at the maximum at 530 nm, Appendix II B, using *iron(III) nitrate solution* in the reference cell. Calculate the content of salicylate as salicylic acid, $C_7H_6O_3$, from the *absorbance* obtained by repeating the operation using 15 mL of a 0.013% w/v solution of *salicylic acid* in 0.02M *hydrochloric acid*, beginning at the words 'Shake 15 mL...'. Each g of salicylic acid is equivalent to 1.530 g of $C_{11}H_{17}NO_3$.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

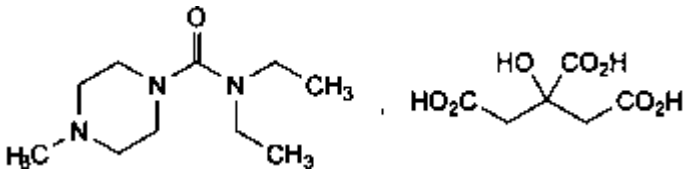
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diethylcarbamazine Citrate

General Notices

(Ph. Eur. monograph 0271)



$C_{16}H_{29}N_3O_8$ 391.4 *1642-54-2*

Action and use

Antihelminthic.

Preparation

Diethylcarbamazine Tablets

Ph Eur

DEFINITION

N,*N*-Diethyl-4-methylpiperazine-1-carboxamide dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, slightly hygroscopic.

Solubility

Very soluble in water, soluble in ethanol (96 per cent), practically insoluble in acetone.

mp

About 138 °C, with decomposition.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *diethylcarbamazine citrate CRS*.

B. Examine the chromatograms obtained in the test for impurities A and B.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.1 g in 5 mL of *water R*. The solution gives the reaction of citrates (2.3.1).

TESTS

Solution S

Shake 2.5 g with *water R* until dissolved and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Impurities A and B

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.5 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 0.1 g of *diethylcarbamazine citrate CRS* in *methanol R* and dilute to 2.0 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of methylpiperazine R (impurity A) in *methanol R* and dilute to 100 mL with the same solvent.

Reference solution (c) Dissolve 10 mg of *dimethylpiperazine R* (impurity B) in *methanol R* and dilute to 100 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *methyl ethyl ketone R*, *methanol R* (5:30:65 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying At 100-105 °C.

www.webofpharma.com

https://thuocngocanh.com/

Detection Expose to iodine vapour for 30 min.

Retardation factors Impurity A = about 0.2; impurity B = about 0.5.

Limits:

— *impurity A*: any spot due to impurity A is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity B*: any spot due to impurity B is not more intense than the corresponding spot in the chromatogram obtained with reference solution (c) (0.2 per cent).

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 31.2 g of potassium dihydrogen phosphate R in water R and dilute to 1000 mL with the same solvent.

Test solution (a) Suspend 0.30 g of the substance to be examined in solution A and dilute to 100 mL with solution A. Filter or centrifuge and use the clear filtrate or supernatant.

Test solution (b) Dissolve 10.0 mg of the substance to be examined in solution A and dilute to 100.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 10 mg of citric acid monohydrate R in solution A and dilute to 10 mL with solution A.

Reference solution (c) To 3 mL of test solution (a) add 0.5 mL of strong hydrogen peroxide solution R and maintain at 80 °C for 3 h. Dilute to 100 mL with solution A.

Reference solution (d) Dissolve 5.0 mg of diethylcarbamazine citrate CRS in solution A and dilute to 50.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase Mix 100 volumes of methanol R2 and 900 volumes of a 10 g/L solution of potassium dihydrogen phosphate R.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time Twice the retention time of diethylcarbamazine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to the citrate.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to diethylcarbamazine (retention time = about 7 min): citrate = about 0.2; degradation product = about 1.6.

System suitability Reference solution (c):

— *resolution*: minimum 5 between the peaks due to diethylcarbamazine and the degradation product.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to the citrate.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 20 µL of test solution (b) and reference solution (d).

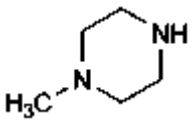
Calculate the percentage content of $C_{16}H_{29}N_3O_8$ from the declared content of *diethylcarbamazine citrate CRS*.

STORAGE

In an airtight container.

IMPURITIES

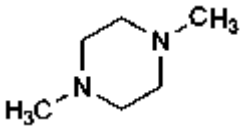
Specified impurities *A, B*.



A. 1-methylpiperazine,

www.webofpharma.com

https://thuocngocanh.com/



B. 1,4-dimethylpiperazine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diethylcarbamazine Tablets

General Notices

Action and use

Antihelminthic.

DEFINITION

Diethylcarbamazine Tablets contain Diethylcarbamazine Citrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diethylcarbamazine citrate, $C_{10}H_{21}N_3O$, $C_6H_8O_7$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 0.15 g of Diethylcarbamazine Citrate add 15 mL of *ethanol (96%)*, shake for 5 minutes, filter and evaporate the filtrate to dryness. To the residue add 10 mL of 2M *sodium hydroxide*, filter if necessary, and extract with three 10-mL quantities of *dichloromethane*. Dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate. The *infrared absorption spectrum* of the oily residue, Appendix II A, is concordant with the *reference spectrum* of diethylcarbamazine (*RS 411*).

B. In the test for related substances, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to citric acid in the chromatogram obtained with solution (3).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *water* and rotate the paddle at 50 revolutions per minute. Carry out the method for *liquid chromatography*, Appendix III D. Dissolve 31.24 g of *potassium dihydrogen orthophosphate* in *water*, add sufficient *water* to produce 1000 mL and mix (solution A). Solution (1) contains 0.0025% w/v of *diethylcarbamazine citrate BPCRS* in solution A.For solution (2) dilute 10 mL of the filtered dissolution medium with an equal volume of a 6.248% w/v solution of *potassium dihydrogen orthophosphate*, filter and dilute with solution A to produce a solution expected to contain about 0.0025% w/v of Diethylcarbamazine Citrate.

The chromatographic procedure described under Assay may be used.

Calculate the total content of diethylcarbamazine citrate, $C_{10}H_{21}N_3O,C_6H_8O_7$, in the medium using the declared content of $C_{10}H_{21}N_3O,C_6H_8O_7$ in *diethylcarbamazine citrate BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

Dimethylpiperazine and methylpiperazine

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 5 volumes of 13.5M *ammonia*, 30 volumes of *butan-2-one* and 65 volumes of *methanol* as the mobile phase. Allow the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.50 g of Diethylcarbamazine Citrate with 20 mL of *methanol* and filter. For solution (2) dissolve 0.05 g of *diethylcarbamazine citrate BPCRS* in *methanol* and dilute to 2.0 mL with the same solvent. For solution (3) dissolve 10 mg of *methylpiperazine* in *methanol* and dilute to 200 mL with the same solvent. For solution (4) dissolve 10 mg of *dimethylpiperazine* in *methanol* and dilute to 200 mL with the same solvent. Dry the plate at 105° and expose to iodine vapour for 30 minutes. Any spots corresponding to methylpiperazine and dimethylpiperazine in the chromatogram obtained with solution (1) are not more intense than the spots in the chromatogram obtained with solutions (3) and (4) respectively (0.2% of each).

Related substances

Weigh and finely powder 20 tablets. Dissolve 31.24 g of *potassium dihydrogen orthophosphate* in *water*, add sufficient *water* to produce 1000 mL and mix (solution A). Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.3 g of Diethylcarbamazine Citrate in 100 mL of solution A, centrifuge and use the clear supernatant liquid. For solution (2) dilute 1 volume of solution (1) to 100 volumes with solution A and further dilute 1 volume of the resulting solution to 10 volumes with solution A to produce a solution containing 0.0003% w/v Diethylcarbamazine Citrate. Solution (3) contains 0.2% w/v of *citric acid* in solution A.

The chromatographic procedure described under Assay may be used.

The area of any *secondary peak* in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%). Disregard any peak with the same retention time as citric acid in the chromatogram obtained with solution (1).

ASSAY

Weigh and finely powder 20 tablets. Dissolve 31.24 g of *potassium dihydrogen orthophosphate* in *water*, add sufficient *water* to produce 1000 mL and mix (solution A). Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dissolve a quantity of the powdered tablets containing 25 mg of Diethylcarbamazine Citrate in 100 mL of solution A, shake and filter. Dilute 10 volumes to 50 volumes with solution A. Solution (2) contains 0.005% w/v *diethylcarbamazine citrate BPCRS* in solution A.

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm x 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry is suitable), (b) as the mobile phase with a flow rate of 0.8 mL per minute a mixture of 100 mL of *methanol* and 900 mL of a solution containing 10 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and (c) a detection wavelength of 220 nm.

Calculate the content of $C_{10}H_{21}N_3O,C_6H_8O_7$ in the tablets using the declared content of $C_{10}H_{21}N_3O,C_6H_8O_7$ in *diethylcarbamazine citrate BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Diethylene Glycol Monoethyl Ether

General Notices

(Ph. Eur. monograph 1198)

$C_6H_{14}O_3$ 134.2 *111-90-0*

Action and use

Excipient.

Ph Eur

DEFINITION

2-(2-Ethoxyethoxy)ethanol, produced by condensation of ethylene oxide and alcohol, followed by distillation.

CHARACTERS

Appearance

Clear, colourless, hygroscopic liquid.

Solubility

Miscible with water, with acetone and with ethanol (96 per cent), miscible in certain proportions with vegetable oils, not miscible with mineral oils.

Relative density

About 0.991.

IDENTIFICATION

A. Refractive index (*2.2.6*): 1.426 to 1.428.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of diethylene glycol monoethyl ether*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acid value (2.5.1)

Maximum 0.1.

Mix 30.0 mL with 30 mL of *alcohol R* previously neutralised with *0.1 M potassium hydroxide* using *phenolphthalein solution R* as indicator. Titrate with *0.01 M alcoholic potassium hydroxide*.

Peroxide value (2.5.5)

Maximum 8.0, determined on 2.00 g.

Related substances

Gas chromatography (2.2.28).

Internal standard solution Dilute 1.00 g of *decane R* to 100.0 mL with *methanol R*.

Test solution To 5.00 g of the substance to be examined, add 0.1 mL of the internal standard solution and dilute to 10.0 mL with *methanol R*.

Reference solution (a) Dilute 25.0 mg of *ethylene glycol monomethyl ether R*, 80.0 mg of *ethylene glycol monoethyl ether R*, 0.310 g of *ethylene glycol R* and 0.125 g of *diethylene glycol R* to 100.0 mL with *methanol R*. To 1.0 mL of this solution add 0.1 mL of the internal standard solution and dilute to 10.0 mL with *methanol R*.

Reference solution (b) Dilute 25.0 mg of *ethylene glycol monoethyl ether R* and 25.0 mg of *ethylene glycol R* to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 5.0 mL with *methanol R*.

Reference solution (c) Dilute 1.00 g of the substance to be examined to 100.0 mL with *methanol R*. To 1.0 mL of this solution add 0.1 mL of the internal standard solution and dilute to 10.0 mL with *methanol R*.

Column:

— *material*: fused silica,

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R* (film thickness 1 µm).

Carrier gas *nitrogen for chromatography R* or *helium for chromatography R*.

Flow rate 2.0 mL/min.

Split ratio 1:80.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Column	0 - 1	120
	1 - 10	120 → 225
	10 - 12	225
Injection port		275
Detector		250

Detection Flame ionisation.

Injection 0.5 µL.

Relative retentions With reference to diethylene glycol monoethyl ether (retention time = about 4 min): ethylene glycol monomethyl ether = about 0.4; ethylene glycol monoethyl ether = about 0.5; ethylene glycol = about 0.55; diethylene glycol = about 1.1.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to ethylene glycol monoethyl ether and to ethylene glycol in the chromatogram obtained with reference solution (b),

— *signal-to-noise ratio*: minimum 3.0 for the peak due to ethylene glycol monomethyl ether in the chromatogram obtained with reference solution (a),

Limits (take into account the impurity/internal standard peak area ratio):

— *ethylene glycol monomethyl ether*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (50 ppm),

— *ethylene glycol monoethyl ether*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (160 ppm),

— *ethylene glycol*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (620 ppm),

— *diethylene glycol*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (250 ppm),

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent).

Ethylene oxide

Head-space gas chromatography (2.2.28).

Test solution To 1.00 g of the substance to be examined in a vial, add 50 µL of *water R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution To 1.00 g of the substance to be examined in a vial, add 50 µL of *ethylene oxide solution R4* and close tightly.

Column:

— *material*: fused silica,

— *size*: *l* = 30 m, Ø = 0.32 mm,

— *stationary phase*: *cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.1 mL/min.

Static head-space conditions which may be used:

— *equilibration temperature*: 80 °C,

— *equilibration time*: 45 min,

— *transfer line temperature*: 110 °C,

— *pressurisation time*: 2 min,

— *injection time*: 12 s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	40
	5 - 18	40 → 200
Injection port		150
Detector		250

Detection Flame ionisation.

Injection 1.0 mL.

The peak due to ethylene oxide is identified by injecting solutions of ethylene oxide of increasing concentration.

Determine the content of ethylene oxide (ppm) in the substance to be examined using the following expression:

$$\frac{S_T \times C}{\left(S_S \times M_T\right) - \left(S_T \times M_S\right)}$$

www.webofpharma.com

https://thuocngocanh.com/

S_T = area of the peak due to ethylene oxide in the chromatogram obtained with the test solution,

S_S = area of the peak due to ethylene oxide in the chromatogram obtained with the reference solution,

M_T = mass of the substance to be examined in the test solution, in grams,

M_S = mass of the substance to be examined in the reference solution, in grams,

C = mass of added ethylene oxide in the reference solution, in micrograms.

Limit:

— *ethylene oxide*: maximum 1 ppm.

Water (*2.5.12*)

Maximum 0.1 per cent, determined on 10.0 g.

STORAGE

Under an inert gas, in an airtight container.

LABELLING

The label states that the substance is stored under an inert gas.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diethylene Glycol Palmitostearate

General Notices

(Ph. Eur. monograph 1415)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of diethylene glycol (2,2′-oxydi(ethan-1-ol)) mono- and diesters of palmitic (hexadecanoic) and stearic (octadecanoic) acids, produced by the condensation of diethylene glycol and stearic acid 50 of vegetable or animal origin (see *Stearic acid (1474)*).

Content

— *monoesters*: 45.0 per cent to 60.0 per cent;

— *diesters*: 35.0 per cent to 55.0 per cent.

CHARACTERS

Appearance

White or almost white, waxy solid.

Solubility

Practically insoluble in water, soluble in acetone and in hot ethanol (96 per cent).

IDENTIFICATION

A. Melting point (see Tests).

B. Composition of fatty acids (see Tests).

C. It complies with the assay (content of monoesters).

TESTS

Melting point (*2.2.15*)

43 °C to 50 °C.

Acid value (2.5.1)

www.webofpharma.com

https://thuocngocanh.com/

Acid value (*2.5.1*)

Maximum 4.0.

Iodine value (*2.5.4*)

Maximum 3.0.

Saponification value (*2.5.6*)

155 to 180, determined on 2.0 g.

Composition of fatty acids (*2.4.22, Method A*)

Use the mixture of calibrating substances in Table 2.4.22.-1.

Composition of the fatty-acid fraction of the substance:

— *stearic acid*: 40.0 per cent to 60.0 per cent;

— *sum of contents of palmitic acid and stearic acid*: minimum 90.0 per cent.

Free diethylene glycol

Maximum 2.5 per cent, determined as prescribed under Assay.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g. Use a mixture of equal volumes of *methanol R* and *methylene chloride R* as the solvent.

Total ash (*2.4.16*)

Maximum 0.1 per cent.

ASSAY

Size-exclusion chromatography (*2.2.30*).

Test solution In a 15 mL flask, weigh 0.200 g (*m*). Add 5.0 mL of *tetrahydrofuran R* and shake to dissolve. Heat gently, if necessary. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

Reference solutions In four 15 mL flasks, weigh respectively 2.5 mg, 5.0 mg, 10.0 mg and 20.0 mg of *diethylene glycol R*. Add 5.0 mL of *tetrahydrofuran R* and shake to dissolve. Weigh the flasks again and calculate the concentration of diethylene glycol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7.5 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1 mL/min.

Detection Differential refractometer.

Injection 40 µL.

Relative retention With reference to diethylene glycol: diesters = about 0.78; monoesters = about 0.84.

Calculations:

— *free diethylene glycol*: from the calibration curve obtained with the reference solutions, determine the concentration of diethylene glycol (*C*) in milligrams per gram in the test solution and calculate the percentage content of free diethylene glycol (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 270}{56.11 \times 10}$$

I_A = acid value (see Tests);

270 = average rounded molar mass of palmitic acid and stearic acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

— *monoesters*: calculate the percentage content of monoesters using the following expression:

$$\left[\frac{X}{X+Y}(100 - A - B)\right] - D$$

A = percentage content of free diethylene glycol;

B = percentage content of water (see Tests);

D = percentage content of free fatty acids;

X = area of the peak due to monoesters and free fatty acids;

Y = area of the peak due to diesters.

— *diesters*: calculate the percentage content of diesters using the following expression:

$$\frac{Y}{X+Y}(100 - A - B)$$

STORAGE

Protected from light.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Diethylstilbestrol

General Notices

(Ph. Eur. monograph 0484)

Removed in version 11.1

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diethylstilbestrol Tablets

General Notices

Action and use

Estrogen.

DEFINITION

Diethylstilbestrol Tablets contain Diethylstilbestrol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diethylstilbestrol, $C_{18}H_{20}O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 3 mg of Diethylstilbestrol with *ether*, filter and evaporate the filtrate to dryness. The residue complies with the following tests.

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.002% w/v solution in *absolute ethanol* exhibits a maximum only at 241 nm.

B. The *light absorption*, Appendix II B, in the range 230 to 450 nm of the irradiated solution prepared as directed in the Assay exhibits two maxima, at 292 nm and 418 nm.

C. Dissolve 0.5 mg in 0.2 mL of *glacial acetic acid*, add 1 mL of *orthophosphoric acid* and heat in a water bath for 3 minutes. A deep yellow colour is produced which almost disappears on dilution with 3 mL of *glacial acetic acid* (distinction from dienoestrol).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 5 mg of Diethylstilbestrol add 50 mL of *absolute ethanol*, shake for 15 minutes, add sufficient *absolute ethanol* to produce 100 mL and centrifuge. Dilute 20 mL of the clear supernatant liquid to 50 mL with *absolute ethanol* and to 25 mL of the resulting solution add 25 mL of a solution prepared by dissolving 1 g of *dipotassium hydrogen orthophosphate* in 55 mL of *water*. Transfer a portion of the mixture to a 1 cm, closed quartz cell, place the cell 10 cm from a 15-watt, short-wave, ultraviolet lamp and irradiate for 10 minutes. Measure the *absorbance* of the irradiated solution at the maximum at 418 nm, Appendix II B, and calculate the content of $C_{18}H_{20}O_2$ from the *absorbance* obtained by repeating the operation using *diethylstilbestrol BPCRS* in place of the powdered tablets.

STORAGE

www.webofpharma.com

https://thuathuocngocanh.com/

Diethylstilbestrol Tablets should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diflucortolone Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Diflucortolone Cream contains Diflucortolone Valerate in a suitable non-oily basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of diflucortolone valerate, $C_{27}H_{36}F_2O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel 60 F_{254} precoated plate (Merck silica gel 60 plates are suitable) and a mixture of 2 volumes of *diethylamine*, 50 volumes of *cyclohexane* and 50 volumes of *ethyl acetate* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) disperse a quantity of the cream containing 1 mg of Diflucortolone Valerate in 5 mL of *dichloromethane* by heating on a water bath, shake vigorously for 15 seconds, cool in ice, filter the dispersion and use the filtrate. Solution (2) contains 0.02% w/v of *diflucortolone valerate BPCRS* in *dichloromethane*. Solution (3) contains a mixture of equal volumes of solutions (1) and (2). Develop the chromatogram twice drying the plate in air for 15 minutes between developments. After removal of the plate, allow it to dry in air for 15 minutes and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to diflucortolone valerate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, injecting 20 µL of each of the following solutions. For solution (1) dissolve 20 mg of *diflucortolone valerate BPCRS* in a 0.02% w/v solution of *clocortolone hexanoate BPCRS* (internal standard) in *methanol* and dilute to 200 mL with the internal standard solution. Add 30 mL of *methanol* to 10 mL of the resulting solution and dilute to 50 mL with *water*. For solution (2) add 40 mL of *methanol* to a quantity of the cream containing 1 mg of Diflucortolone Valerate, disperse by heating on a water bath at 60° for 5 minutes and shake for 30 seconds. Add 10 mL of *water*, cool in ice for 10 minutes and filter. Prepare solution (3) in the same manner as solution (2) but adding 10 mL of a 0.02% w/v solution of *clocortolone hexanoate BPCRS* in *methanol* and 30 mL of *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic procedure may be carried out using (a) a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable), (b) as the mobile phase with a flow rate of 2 mL per minute a mixture of 250 volumes of *water* and 750 volumes of *methanol* and (c) a detection wavelength of 254 nm.

Calculate the content of $C_{27}H_{36}F_2O_5$ in the cream using the declared content of $C_{27}H_{36}F_2O_5$ in *diflucortolone valerate BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diflucortolone Oily Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Diflucortolone Oily Cream contains Diflucortolone Valerate in a suitable oily basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of diflucortolone valerate, $C_{27}H_{36}F_2O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel 60 F_{254} precoated plate (Merck silica gel 60 plates are suitable) and a mixture of 2 volumes of *diethylamine*, 50 volumes of *cyclohexane* and 50 volumes of *ethyl acetate* as the mobile phase. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) disperse a quantity of the cream containing 1 mg of Diflucortolone Valerate in 10 mL of *dichloromethane* by heating on a water bath, shake vigorously for 1 minute, cool in ice, filter the dispersion and use the filtrate. Solution (2) contains 0.01% w/v of *diflucortolone valerate BPCRS* in *dichloromethane*. Solution (3) contains a mixture of equal volumes of solutions (1) and (2). Develop the chromatogram twice drying the plate in air for 15 minutes between developments. After removal of the plate, allow it to dry in air for 15 minutes and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to diflucortolone valerate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, injecting 20 µL of each of the following solutions. For solution (1) dissolve 20 mg of *diflucortolone valerate BPCRS* in a 0.02% w/v solution of *clocortolone hexanoate BPCRS* (internal standard) in *methanol* and dilute to 200 mL with the internal standard solution. Add 30 mL of *methanol* to 10 mL of the resulting solution and dilute to 50 mL with *water*. For solution (2) add 40 mL of *methanol* to a quantity of the cream containing 1 mg of Diflucortolone Valerate, disperse by heating on a water bath at 60° for 5 minutes and shake for 30 seconds. Add 10 mL of *water*, cool in ice for 10 minutes and filter. Prepare solution (3) in the same manner as solution (2) but adding 10 mL of a 0.02% w/v solution of *clocortolone hexanoate BPCRS* in *methanol* and 30 mL of *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic procedure described under Diflucortolone Cream may be used.

Calculate the content of $C_{27}H_{36}F_2O_5$ in the cream using the declared content of $C_{27}H_{36}F_2O_5$ in *diflucortolone valerate BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diflucortolone Ointment

General Notices

Action and use

Glucocorticoid.

DEFINITION

Diflucortolone Ointment contains Diflucortolone Valerate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of diflucortolone valerate, $C_{27}H_{36}F_2O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the ointment containing 1 mg of Diflucortolone Valerate in 5 mL of *dichloromethane* by heating on a water bath, shake vigorously for 15 seconds, cool in ice, filter the dispersion and use the filtrate.

(2) 0.02% w/v of *diflucortolone valerate BPCRS* in *dichloromethane*.

(3) A mixture of equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* 60 GF_{254} (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air for 15 minutes.

(f) Place the plate in the same tank using the mobile phase as described below.

(g) After removal of the plate, dry in air for 15 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of *diethylamine*, 50 volumes of *cyclohexane* and 50 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

www.webofpharma.com

https://nhathuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to diflucortolone valerate in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve 20 mg of *diflucortolone valerate BPCRS* in a 0.02% w/v solution of *clocortolone hexanoate BPCRS* (internal standard) in *methanol* and dilute to 200 mL with the internal standard solution. Add 30 mL of *methanol* to 10 mL of the resulting solution and dilute to 50 mL with *water*.

(2) Shake a quantity of the ointment containing 1 mg of Diflucortolone Valerate with 10 mL of a 0.02% w/v solution of *clocortolone hexanoate BPCRS* in *methanol* and add 30 mL of *methanol*. Disperse by heating on a water bath at 60° for 5 minutes and shake for 30 seconds. Add 10 mL of *water*, cool in ice for 10 minutes and filter.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

250 volumes of *water* and 750 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{36}F_2O_5$ in the ointment using the declared content of $C_{27}H_{36}F_2O_5$ in *diflucortolone valerate BPCRS*.

© Crown Copyright 2022

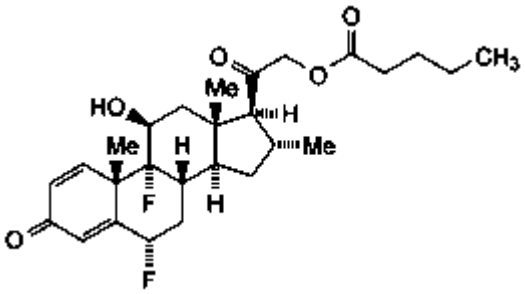
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diflucortolone Valerate

General Notices



$C_{27}H_{36}F_2O_5$ 478.6 *59198-70-8*

Action and use

Glucocorticoid.

Preparations

Diflucortolone Cream

Diflucortolone Oily Cream

Diflucortolone Ointment

DEFINITION

Diflucortolone Valerate is 6α,9α-difluoro-3,20-dioxo-11β-hydroxy-16α-methylpregna-1,4-dien-21-yl valerate. It contains not less than 97.0% and not more than 102.0% of $C_{27}H_{36}F_2O_5$, calculated with reference to the dried substance.

CHARACTERISTICS

A white to creamy white, crystalline powder.

Practically insoluble in *water*; freely soluble in *dichloromethane* and in *1,4-dioxan*; slightly soluble in *methanol*; sparingly soluble in *ether*.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 350 nm of a 0.002% w/v solution in *methanol* exhibits a maximum only at 238 nm. The *absorbance* at the maximum at 238 nm is about 0.69.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of diflucortolone valerate *(RS 100)*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Specific optical rotation

In a 1% w/v solution in *1,4-dioxan*, +98 to +103, Appendix V F, calculated with reference to the dried substance.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, injecting 20 µL of each of the following solutions in a mixture of 25 volumes of *water* and 75 volumes of *acetonitrile*. Solution (1) contains 0.060% w/v of the substance being examined. For solution (2) dilute 1 volume of solution (1) to 100 volumes. Solution (3) contains 0.060% w/v of *diflucortolone valerate impurity standard BPCRS*.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS 2 is suitable), (b) a mixture of equal volumes of *acetonitrile* and *water* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 238 nm. If necessary the composition of the mobile phase may be altered so that the chromatogram obtained with solution (3) shows similar resolution to the reference chromatogram supplied with *diflucortolone valerate impurity standard BPCRS*.

Continue the chromatography for twice the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%) and the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Loss on drying

When dried to constant weight at 105°, loses not more than 0.5% of its weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following three solutions in a mixture of 25 volumes of *water* and 75 volumes of *acetonitrile* containing (1) 0.03% w/v of the substance being examined, (2) 0.03% w/v of *diflucortolone valerate BPCRS* and (3) 0.03% w/v of *diflucortolone valerate impurity standard BPCRS*.

The chromatographic procedure described under Related substances may be used.

Calculate the content of $C_{27}H_{36}F_2O_5$ from the declared content of $C_{27}H_{36}F_2O_5$ in *diflucortolone valerate BPCRS*.

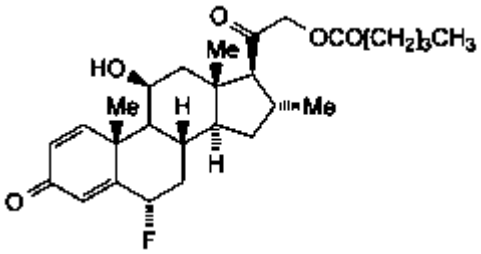
STORAGE

Diflucortolone Valerate should be protected from light.

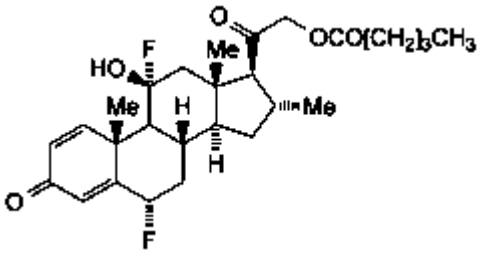
IMPURITIES

www.webofpharma.com

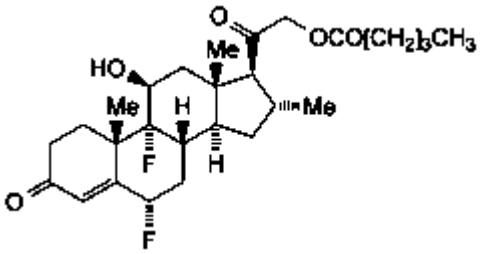
https://thuocngocanh.com/



A. 6α-fluoro-3,20-dioxo-11β-hydroxy-16α-methylpregna-1,4-dien-21-yl valerate,



B. 6α,12α-difluoro-3,20-dioxo-11β-hydroxy-16α-methylpregna-1,4-dien-21-yl valerate,



C. 6α,9α-difluoro-3,20-dioxo-11β-hydroxy-16α-methylpregna-1,4-dien-21-yl valerate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

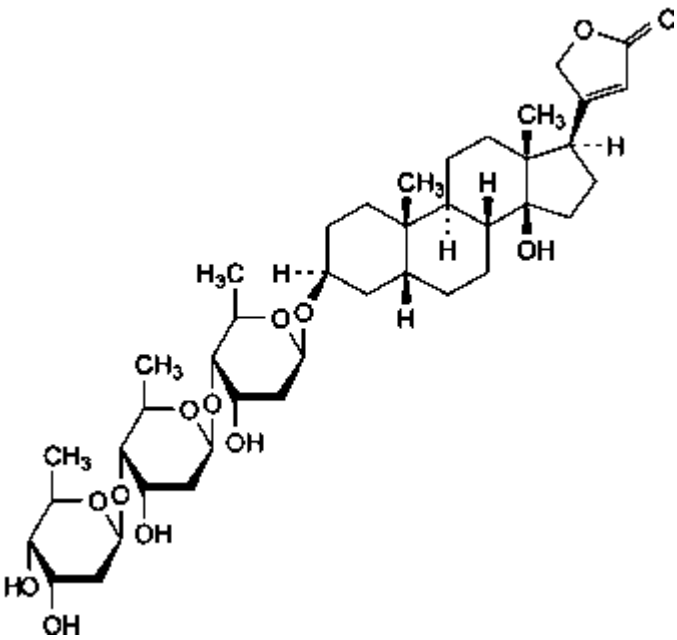
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Digitoxin

General Notices

(Ph. Eur. monograph 0078)



$C_{41}H_{64}O_{13}$ 765 *71-63-6*

Action and use

Na/K-ATPase inhibitor; cardiac glycoside.

Ph Eur

DEFINITION

Digitoxin contains not less than 95.0 per cent and not more than the equivalent of 103.0 per cent of 3β-[(*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14-hydroxy-5β,14β-card-20(22)-enolide, calculated with reference to the dried substance.

CHARACTERS

A white or almost white powder, practically insoluble in water, freely soluble in a mixture of equal volumes of methanol and methylene chloride, slightly soluble in ethanol (96 per cent) and in methanol.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *digitoxin CRS*.

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Suspend about 0.5 mg in 0.2 mL of *alcohol (60 per cent V/V) R*. Add 0.1 mL of *dinitrobenzoic acid solution R* and 0.1 mL of *dilute sodium hydroxide solution R*. A violet colour develops.

D. Dissolve about 0.5 mg in 1 mL of *glacial acetic acid R*, heating gently, allow to cool and add 0.05 mL of *ferric chloride solution R1*. Cautiously add 1 mL of *sulfuric acid R*, avoiding mixing the two liquids. A brown ring develops at the interface and on standing a green, then blue colour passes to the upper layer.

TESTS

Appearance of solution

Dissolve 50 mg in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 10 mL with the same mixture of solvents. The solution is clear (2.2.1) and colourless (2.2.2, *Method I*).

Specific optical rotation (2.2.7)

Dissolve 0.25 g in *chloroform R* and dilute to 10.0 mL with the same solvent. The specific optical rotation is + 16.0 to + 18.5.

Related substances

Examine by thin-layer chromatography (2.2.27), using a *TLC silica gel G plate R*.

Test solution Dissolve 20 mg of the substance to be examined in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 2 mL with the same mixture of solvents.

Reference solution (a) Dissolve 20 mg of *digitoxin CRS* in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 2 mL with the same mixture of solvents.

Reference solution (b) Dilute 0.5 mL of reference solution (a) to 50 mL with a mixture of equal volumes of *methanol R* and *methylene chloride R*.

Reference solution (c) Dissolve 10 mg of *gitoxin CRS* with stirring in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 50 mL with the same mixture of solvents.

Reference solution (d) Dilute 1 mL of reference solution (b) to 2 mL with a mixture of equal volumes of *methanol R* and *methylene chloride R*.

Reference solution (e) Mix 1 mL of reference solution (a) and 1 mL of reference solution (c).

www.webofpharma.com

https://thuocngocanh.com/

Apply to the plate 5 µL of each solution. Develop immediately over a path of 15 cm using a mixture of 15 volumes of *methanol R*, 40 volumes of *cyclohexane R* and 90 volumes of *methylene chloride R*. Dry the plate in a stream of cold air for 5 min. Repeat the development and dry the plate in a stream of cold air for 5 min. Spray with a mixture of 1 volume of *sulfuric acid R* and 9 volumes of *alcohol R* and heat at 130 °C for 15 min. Examine in daylight.

Gitoxin Any spot corresponding to gitoxin in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (c) (2.0 per cent).

Other glycosides Any spot in the chromatogram obtained with the test solution, apart from the principal spot and the spot corresponding to gitoxin, is not more intense than the spot in the chromatogram obtained with reference solution (b) (1.0 per cent).

The test is not valid unless the chromatogram obtained with reference solution (e) shows clearly separated spots corresponding to digitoxin, gitoxin and other glycosides and the spot in the chromatogram obtained with reference solution (d) is clearly visible.

Loss on drying (*2.2.32*)

Not more than 1.5 per cent, determined on 0.500 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on the residue from the test for loss on drying.

ASSAY

Dissolve 40.0 mg in *alcohol R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *alcohol R*. Prepare a reference solution in the same manner, using 40.0 mg of *digitoxin CRS*. To 5.0 mL of each solution add 3.0 mL of *alkaline sodium picrate solution R*, allow to stand protected from bright light for 30 min and measure the absorbance (*2.2.25*) of each solution at the maximum at 495 nm, using as the compensation liquid a mixture of 5.0 mL of *alcohol R* and 3.0 mL of *alkaline sodium picrate solution R* prepared at the same time.

Calculate the content of $C_{41}H_{64}O_{13}$ from the absorbances measured and the concentrations of the solutions.

STORAGE

Store protected from light.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

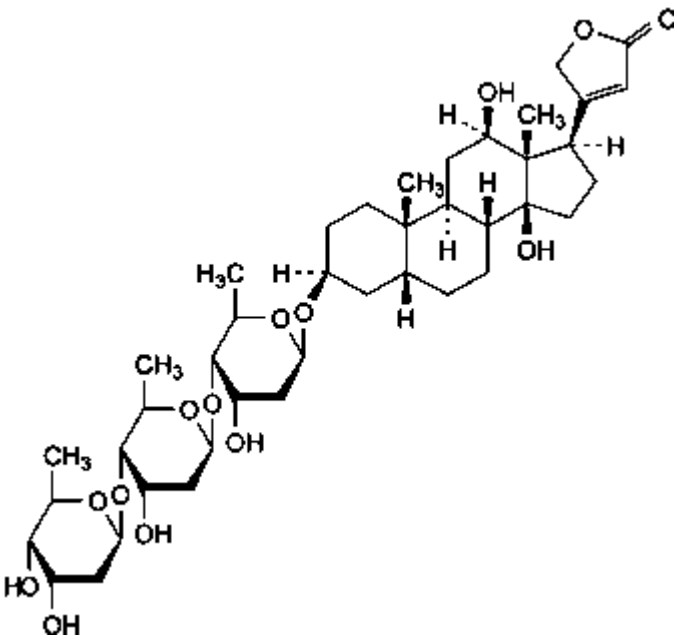
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Digoxin

General Notices

(Ph. Eur. monograph 0079)



$C_{41}H_{64}O_{14}$ 781 *20830-75-5*

Action and use

Na/K-ATPase inhibitor; cardiac glycoside.

Preparations

Digoxin Injection

Paediatric Digoxin Injection

Paediatric Digoxin Oral Solution

Digoxin Tablets

Ph Eur

DEFINITION

3β-[(2,6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide.

www.webofpharma.com

https://thuocngocanh.com/

Content

96.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder, or colourless crystals.

Solubility

Practically insoluble in water, soluble in a mixture of equal volumes of methanol and methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *digoxin CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method I*).

Dissolve 50 mg in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Specific optical rotation (*2.2.7*)

+ 13.9 to + 15.9 (dried substance).

Dissolve 0.50 g in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 25.0 mL with the same mixture of solvents.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in 100.0 mL of *methanol R*.

Reference solution (a) Dissolve 10.0 mg of *digoxin CRS* in *methanol R* and dilute to 20.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*.

Reference solution (c) Dissolve 2.5 mg of *digoxigenin CRS* (impurity C) in *methanol R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dissolve 50.0 mg of *lanatoside C R* (impurity H) in *methanol R* and dilute to 100.0 mL with the same solvent. To 1.0 mL of this solution, add 1.0 mL of the test solution and dilute to 20.0 mL with *methanol R*.

Reference solution (e) Dissolve 5.0 mg of *digoxin for peak identification CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water R* (10:90 *V/V*);

— *mobile phase B*: *water R*, *acetonitrile R* (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	78	22
5 - 15	78 → 30	22 → 70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (b), (c), (d) and (e).

Identification of impurities Use the chromatogram supplied with *digoxin for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities A, B, C, E, F, G and K.

Relative retention With reference to digoxin (retention time = about 4.3 min): impurity C = about 0.3; impurity E = about 0.5; impurity F = about 0.6; impurity G = about 0.8; impurity L = about 1.4; impurity K = about 1.6; impurity B = about 2.2; impurity A = about 2.6.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to impurity H and digoxin.

Limits:

— *impurity F*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.5 per cent);

— *impurity C*: not more than 5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *impurities E, K*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity G*: not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent);

— *impurities A, B*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity L*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *sum of impurities other than A, B, C, E, F, G, K, L*: not more than 0.7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *total*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.5 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

The thresholds indicated under Related Substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying *in vacuo* in an oven.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on the residue obtained in the test for loss on drying.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{41}H_{64}O_{14}$ from the declared content of *digoxin CRS*.

STORAGE

Protected from light.

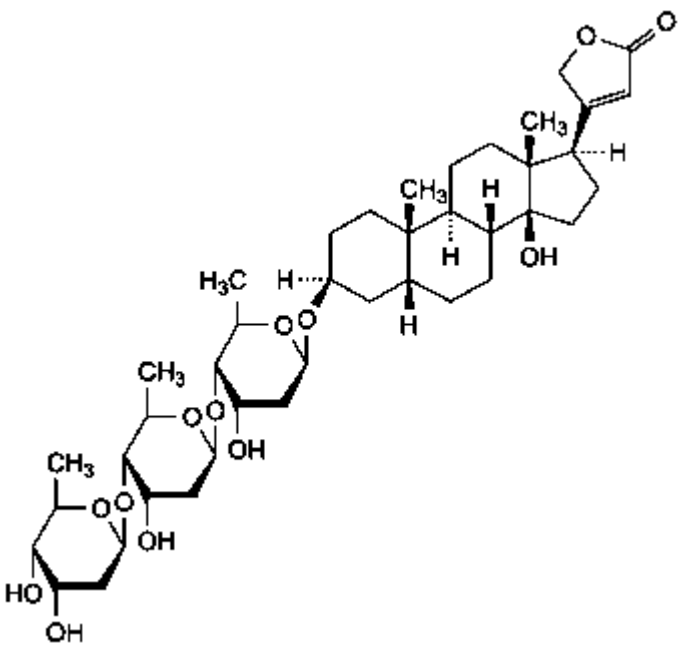
IMPURITIES

Specified impurities *A, B, C, E, F, G, K, L.*

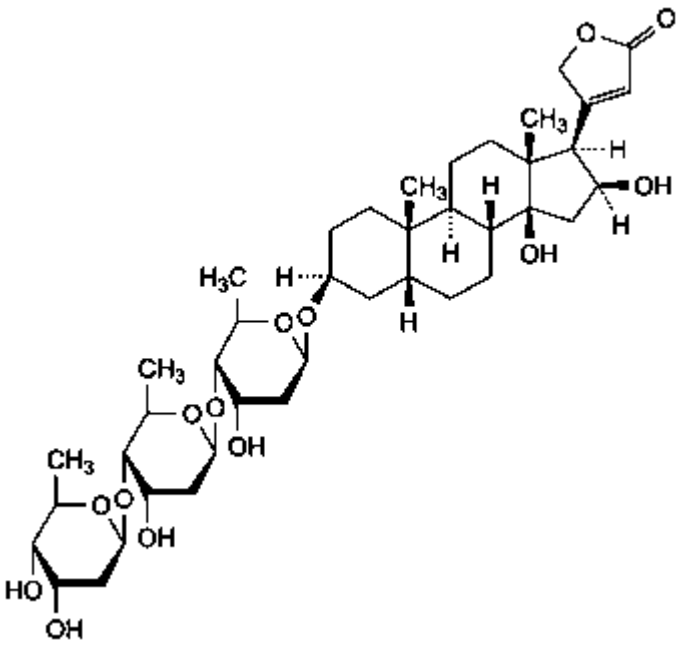
www.webofpharma.com

https://thuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, H, I, J.



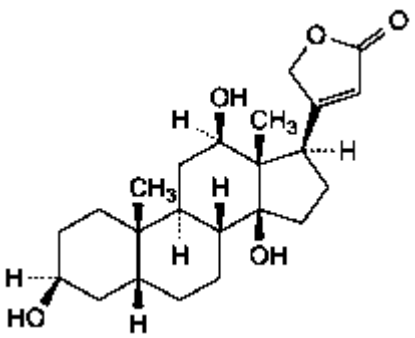
A. 3β-[(2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14-hydroxy-5β-card-20(22)-enolide (digitoxin),



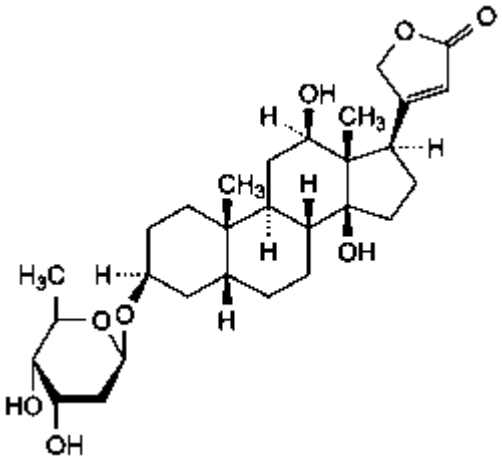
B. 3β-[(2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-14,16β-dihydroxy-5β-card-20(22)-enolide (gitoxin),

www.webofpharma.com

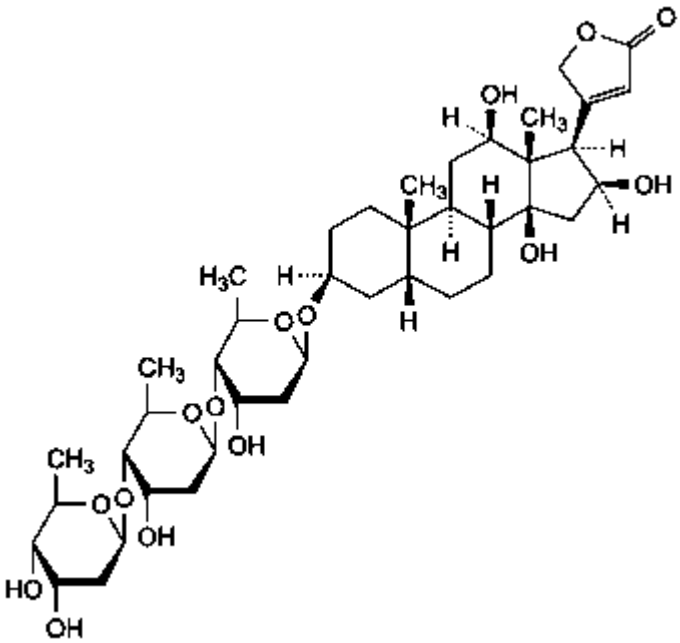
https://thuocngocanh.com/



C. 3β,12β,14-trihydroxy-5β-card-20(22)-enolide (digoxigenin),



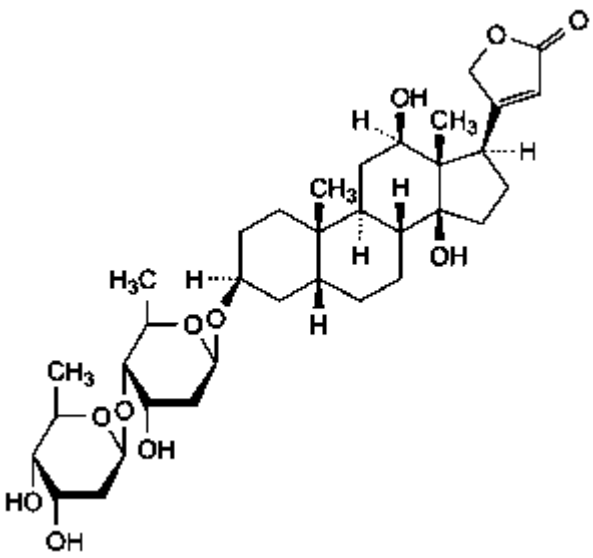
D. 3β-(2,6-dideoxy-β-D-*ribo*-hexopyranosyloxy)-12β,14-dihydroxy-5β-card-20(22)-enolide (digoxigenin monodigitoxoside),



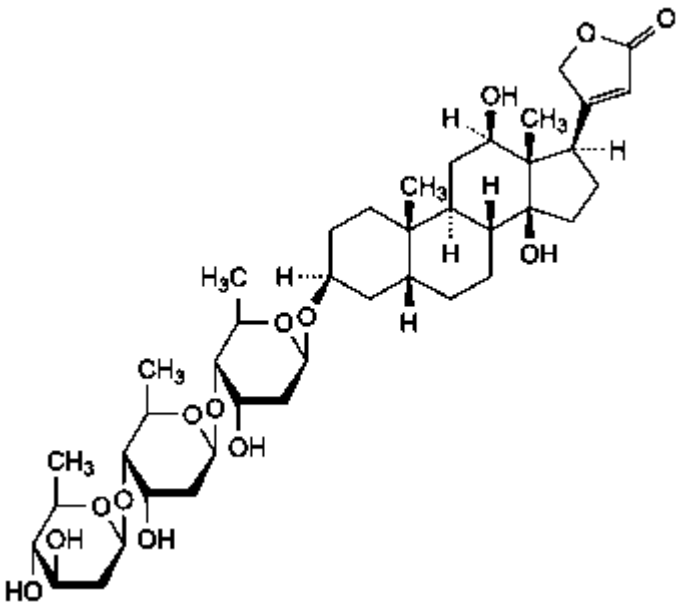
E. 3β-[(2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14,16β-trihydroxy-5β-card-20(22)-enolide (diginatin),

www.webofpharma.com

https://thuocngocanh.com/



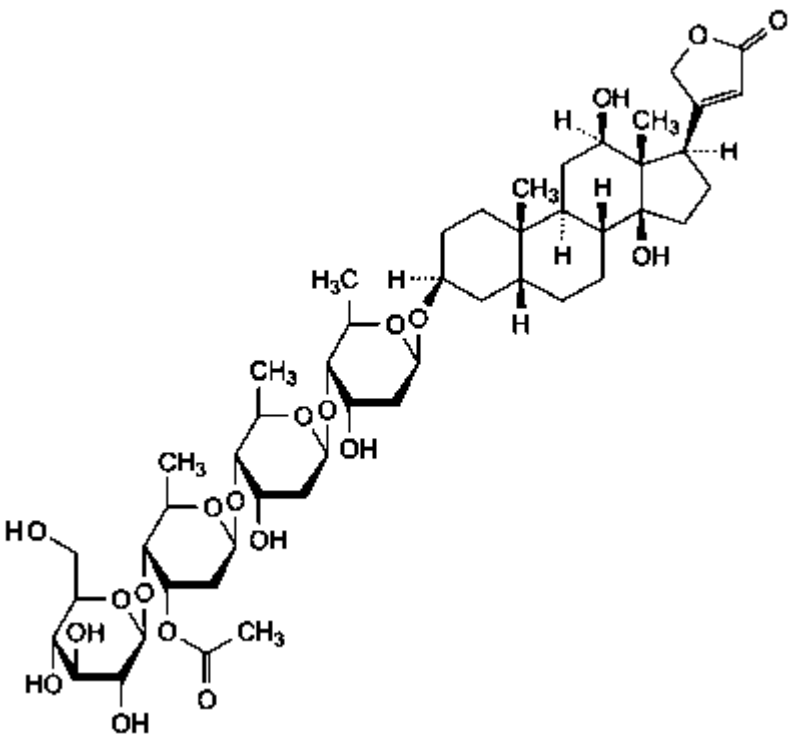
F. 3β-[(2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (digoxigenin bisdigitoxoside),



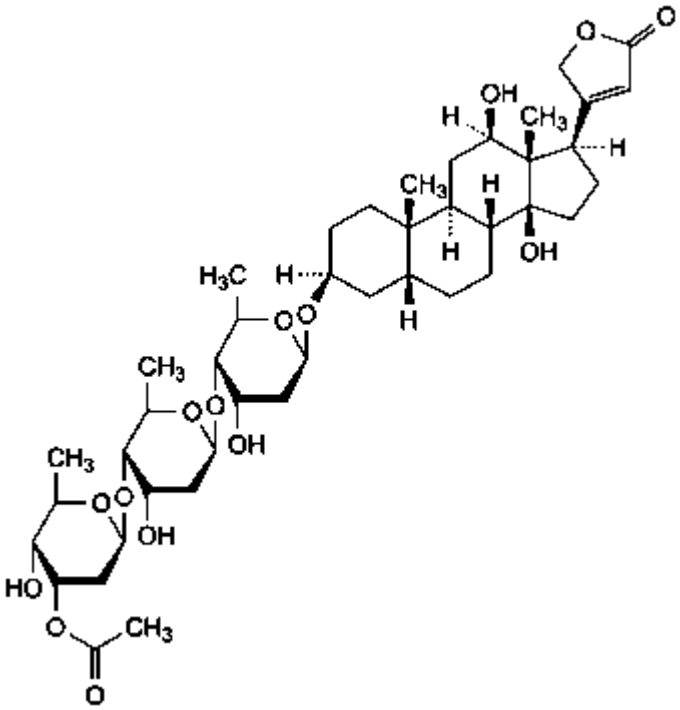
G. 3β-[(2,6-dideoxy-β-D-*arabino*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (neodigoxin),

www.webofpharma.com

https://thuocngocanh.com/



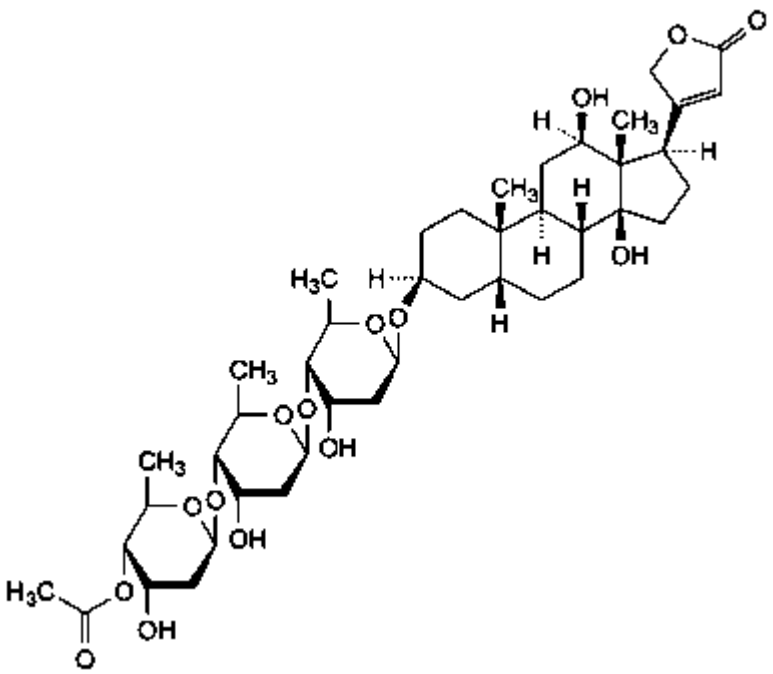
H. 3β-[(β-D-glucopyranosyl-(1→4)-3-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (lanatoside C),



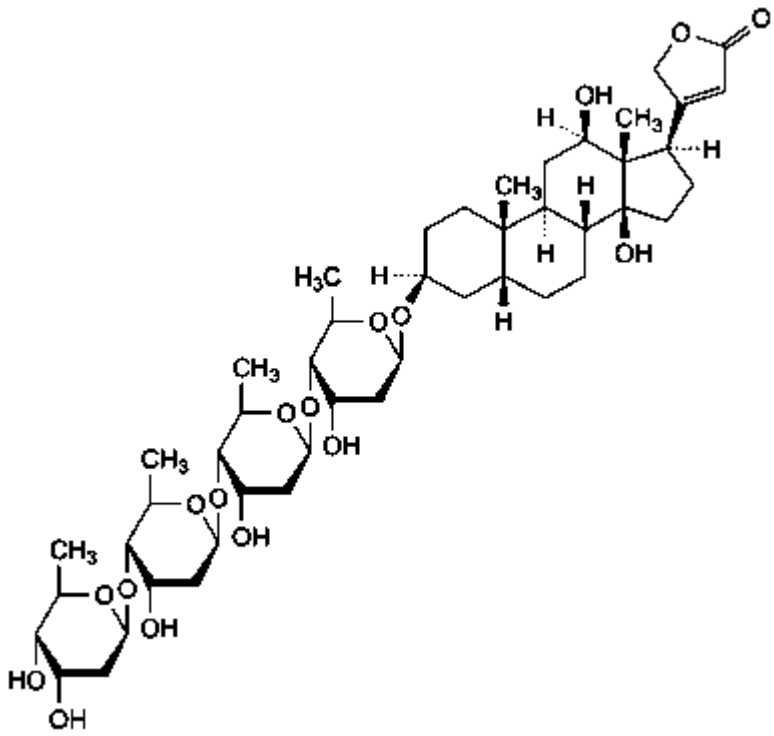
I. 3β-[(3-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (α-acetyldigoxin),

www.webofpharma.com

https://thuocngocanh.com/



J. 3β-[(4-*O*-acetyl-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (β-acetyldigoxin),



K. 3β-[(2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide (digoxigenin tetrakisdigitoxoside),

L. unknown structure.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Digoxin Injection

General Notices

Action and use

Na /K-ATPase inhibitor; cardiac glycoside.

DEFINITION

Digoxin Injection contains Digoxin 0.025% w/v in a suitable vehicle.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of digoxin, $C_{41}H_{64}O_{14}$

0.0237 to 0.0263% w/v.

IDENTIFICATION

Evaporate 2 mL to dryness, dissolve the residue in 1 mL of *glacial acetic acid* containing 0.01% w/v of *iron(iii) chloride* and cautiously add 1 mL of *sulfuric acid* without mixing. A brown ring, free from red colour, is produced at the interface and, after a short time, an indigo colour is produced in the upper layer.

TESTS

Acidity or alkalinity

pH, 6.7 to 7.3, Appendix V L.

ASSAY

Transfer 20 mL to a separating funnel containing 10 mL of *water*. Make alkaline with 5M *ammonia* and extract with four 25 mL quantities of *chloroform*. Wash each extract with the same 10 mL of *water*. Evaporate the combined chloroform extracts to dryness on a water bath, dry the residue at 105° for 15 minutes, cool, dissolve the residue in 5 mL of a mixture of 65 volumes of *chloroform* and 35 volumes of *methanol* and add 20 mL of *glacial acetic acid* (solution A). To 5 mL of a 0.2% w/v solution of *digoxin EPCRS* in *glacial acetic acid* add 10 mL of a mixture of 65 volumes of *chloroform* and 35 volumes of *methanol* and sufficient *glacial acetic acid* to produce 50 mL (solution B). Dilute 5 mL of solution A to 25 mL with *digoxin reagent*, mix, allow to stand for 2 hours and measure the *absorbance* of the resulting solution at 590 nm, Appendix II B, using *water* in the reference cell. Calculate the content of $C_{41}H_{64}O_{14}$ from the *absorbance* obtained by treating 5 mL of solution B at the same time and in the same manner.

STORAGE

www.webofpharma.com

https://thuathuocngocanh.com/

Digoxin Injection should be protected from light.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Digoxin Tablets

General Notices

Action and use

Na/K-ATPase inhibitor; cardiac glycoside.

DEFINITION

Digoxin tablets contain digoxin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of digoxin, $C_{41}H_{64}O_{14}$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

To a quantity of the powdered tablets containing 0.25 mg of Digoxin, add 1 mL of *glacial acetic acid* containing 0.01% w/v of *iron(III) chloride hexahydrate*, shake for a few minutes, filter through sintered glass and cautiously add 1 mL of *sulfuric acid* without mixing. A brown ring, free from red colour, is produced at the interface and, after a short time, an indigo colour is produced in the upper layer.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, placing six tablets in the basket, using as the medium 600 mL of *water* freshly prepared by distillation and rotating the basket at 120 revolutions per minute for 60 minutes. Withdraw a sample of 5 mL of the medium. Filter the sample through a membrane filter disc with a nominal pore size not greater than 0.8 µm, discarding the first 1 mL of the filtrate, and transfer 1 mL to a 10 mL graduated flask. Add 3 mL of a 0.1% w/v solution of L-*ascorbic acid* in *methanol* and 0.2 mL of a 0.009M solution of hydrogen peroxide, prepared by accurately diluting *hydrogen peroxide solution (100 vol)* that has been standardised by titration with 0.02M *potassium permanganate VS*, mix and dilute to volume with *hydrochloric acid*. After exactly 2 hours measure the *fluorescence* of the solution, Appendix II E, using an excitation wavelength of 360 nm and an emission wavelength of 490 nm and setting the instrument to zero with *water* and to 100 with a solution prepared at the same time as the test solution in the following manner. Dilute 2.5 mL of a 0.100% w/v solution of *digoxin EPCRS* in *ethanol (80%)* to 100 mL with *water*, dilute the resulting solution further with *water* to produce a solution containing in 1 mL an amount of Digoxin equal to one-hundredth of the strength of the tablets being examined, transfer 1 mL of the solution to a 10 mL graduated flask and carry out the operation described above, beginning at the words ‘Add 3 mL ... ‘. The amount of digoxin, $C_{41}H_{64}O_{14}$, per tablet in solution is not less than 75% of the stated amount.

www.webofpharma.com

https://thuocngocanh.com/

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Digoxin comply with the requirements stated under Tablets using the following method of analysis. For tablets containing 0.125 mg of digoxin, place one tablet in 5 mL of *water* at 37°, agitate to disintegrate, add 28 mL of *ethanol (96%)*, shake for 1 hour and add sufficient *ethanol (80%)* to produce 50 mL. For tablets containing more or less than 0.125 mg of Digoxin carry out the same procedure but using correspondingly greater or smaller quantities of *water*, *ethanol (96%)* and *ethanol (80%)*. Filter the resulting solution through a suitable membrane filter disc with a nominal pore size not greater than 0.8 µm, discarding the first few mL of the filtrate, and transfer 1.0 mL to a 10 mL graduated flask. Add 3 mL of a 0.1% w/v solution of L-*ascorbic acid* in *methanol*, 0.2 mL of a 0.009M solution of hydrogen peroxide prepared by accurately diluting *hydrogen peroxide solution (100 vol)* that has been standardised by titration with 0.02M *potassium permanganate VS*, mix and dilute to volume with *hydrochloric acid*. After exactly 2 hours measure the *fluorescence* of the solution, Appendix II E, using an excitation wavelength of 360 nm and an emission wavelength of 490 nm and setting the instrument to zero with *water*. Calculate the content of digoxin, $C_{41}H_{64}O_{14}$, from the *fluorescence* obtained by carrying out the operation at the same time using a solution containing 2.5 µg per mL of *digoxin EPCRS* in *ethanol (80%)* and beginning at the words 'transfer 1.0 mL ...'.

ASSAY

Weigh and finely powder 20 tablets. To a quantity of the powder containing 1.25 mg of Digoxin add 3 mL of *water*, swirl to disperse the powder and allow to stand for 10 minutes swirling occasionally. Add 25 mL of *glacial acetic acid*, shake for 1 hour and filter (Whatman No. 1 paper is suitable), discarding the first few mL. To 4 mL of the filtrate add 1 mL of *dimethyl sulfoxide*, dilute to 25 mL with *xanthydrol reagent*, mix well and allow to stand in the dark for 4 hours (solution A). At the same time prepare two further solutions in the same manner but using for solution B 4 mL of *digoxin standard solution* and for solution C 4 mL of a mixture of 25 volumes of *glacial acetic acid* and 3 volumes of *water* and beginning at the words 'add 1 mL of *dimethyl sulfoxide* ...'. Measure the *absorbances* of solutions A and B at the maximum at 545 nm, Appendix II B, using solution C in the reference cell.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dihydrocodeine Injection

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Dihydrocodeine Injection is a sterile solution of Dihydrocodeine Tartrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of dihydrocodeine tartrate, $C_{18}H_{23}NO_3,C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Carry out the following procedure protected from light. To a volume of the injection containing 0.1 g of Dihydrocodeine Tartrate add 2 mL of *water*, mix with the aid of ultrasound and filter. Add 4 mL of *dichloromethane* and 0.5 mL of *strong sodium hydroxide solution* to the filtrate, mix and centrifuge. Isolate the lower layer and evaporate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of dihydrocodeine (*RS 102*).

TESTS

Acidity

pH, 3.0 to 4.5, Appendix V L.

Related substances

Carry out the following test protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the injection to produce a solution containing 0.1% w/v of Dihydrocodeine Tartrate.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Hypersil Gold C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 284 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of dihydrocodeine.

MOBILE PHASE

To 1.0 g of *sodium heptanesulfonate*, add 10 mL of *glacial acetic acid* and 4 mL of a solution containing 5 mL of *triethylamine* diluted to 25 mL with a mixture of equal volumes of *acetonitrile* and *water*. Add 170 mL of *acetonitrile* and dilute to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions, the retention relative to dihydrocodeine (retention time about 11 minutes) of codeine is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to codeine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peaks* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the following procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a volume of the injection containing 25 mg of Dihydrocodeine Tartrate to 25 mL with mobile phase and filter. Dilute 1 volume to 10 volumes.

(2) 0.01% w/v of *dihydrocodeine tartrate BPCRS*.

(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{23}NO_3,C_4H_6O_6$, in the injection, using the declared content of $C_{18}H_{23}NO_3,C_4H_6O_6$ in *dihydrocodeine tartrate BPCRS*.

STORAGE

Dihydrocodeine Injection should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Dihydrocodeine Tartrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dihydrocodeine Oral Solution

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Dihydrocodeine Oral Solution is a solution of Dihydrocodeine Tartrate in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of dihydrocodeine tartrate, $C_{18}H_{23}NO_3$, $C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Carry out the following procedure protected from light. To a volume of the oral solution containing 20 mg of Dihydrocodeine Tartrate add 10 mL of *water* and extract with two 25-mL quantities of *cyclohexane*. Discard the cyclohexane extracts, add 3 mL of 5M *sodium hydroxide* to the aqueous layer, mix and extract with 25 mL of *cyclohexane*. Wash the cyclohexane layer with 10 mL of *water*, shake with *anhydrous sodium sulfate* and filter. Wash the filter with *cyclohexane* and evaporate the combined filtrate and washings to dryness. Dissolve the residue in 1 mL of *dichloromethane* and apply 0.2 mL dropwise on to the surface of a disc prepared using 0.3 g of *potassium bromide*, allowing the solvent to evaporate between applications, and dry the disc at 50° for 2 minutes. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of dihydrocodeine *(RS 102)*.

TESTS

Related substances

Carry out the following test protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the oral solution to produce a solution containing 0.1% w/v of Dihydrocodeine Tartrate.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Hypersil Gold C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 284 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A To 1.0 g of *sodium heptanesulfonate*, add 10 mL of *glacial acetic acid* and 4 mL of a solution containing 5 mL of *triethylamine* diluted to 25 mL with a mixture of equal volumes of *acetonitrile* and *water*. Add 170 mL of *acetonitrile* and dilute to 1000 mL with *water*.

Mobile phase B *acetonitrile*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-25	100→20	0→80	linear gradient
25-40	20	80	isocratic
40-45	20→100	80→0	linear gradient
45-50	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention relative to dihydrocodeine (retention time about 11 minutes) of codeine is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to codeine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the following procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a weighed quantity of the oral solution containing 25 mg of Dihydrocodeine Tartrate in 25 mL of mobile phase A and filter. Dilute 1 volume to 10 volumes with mobile phase A.

(2) 0.01% w/v of *dihydrocodeine tartrate BPCRS* in *water*.

(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

Use the conditions described under Related substances.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{18}H_{23}NO_3$, $C_4H_6O_6$, weight in volume, using the declared content of $C_{18}H_{23}NO_3$, $C_4H_6O_6$ in *dihydrocodeine tartrate BPCRS*.

STORAGE

Dihydrocodeine Oral Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Dihydrocodeine Tartrate.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dihydrocodeine Prolonged-release Tablets

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Dihydrocodeine Prolonged-release Tablets contain Dihydrocodeine Tartrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Dihydrocodeine Tartrate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dihydrocodeine tartrate, $C_{18}H_{23}NO_3,C_4H_6O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Carry out the following procedure protected from light. Mix a quantity of the powdered tablets containing 0.1 mg of Dihydrocodeine Tartrate and 4 mL of *water* with the aid of ultrasound and filter. Add 4 mL of *dichloromethane* and 0.5 mL of *strong sodium hydroxide solution* to the filtrate, mix and centrifuge. Isolate the lower layer and evaporate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of dihydrocodeine (*RS 102*).

TESTS

Related substances

Carry out the following test protected from light.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix a quantity of the powdered tablets containing 50 mg of Dihydrocodeine Tartrate and 25 mL of the mobile phase with the aid of ultrasound, dilute to 50 mL and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5µm) (Hypersil Gold C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 284 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of dihydrocodeine.

MOBILE PHASE

To 1.0 g of *sodium heptanesulfonate*, add 10 mL of *glacial acetic acid* and 4 mL of a solution containing 5 mL of *triethylamine* diluted to 25 mL with a mixture of equal volumes of *acetonitrile* and *water*. Add 170 mL of *acetonitrile* and dilute to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions, the retention relative to dihydrocodeine (retention time about 11 minutes) of codeine is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to codeine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the following procedure protected from light.

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dissolve a quantity of the powdered tablets containing 50 mg of Dihydrocodeine Tartrate in 25 mL of mobile phase with the aid of ultrasound and dilute to 50 mL. Dilute 1 volume to 10 volumes.

(2) 0.01% w/v of *dihydrocodeine tartrate BPCRS*.

(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{23}NO_3,C_4H_6O_6$ in the tablets using the declared content of $C_{18}H_{23}NO_3,C_4H_6O_6$ in *dihydrocodeine tartrate BPCRS*.

STORAGE

Dihydrocodeine Prolonged-release Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Dihydrocodeine Tartrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dihydrocodeine Tablets

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Dihydrocodeine Tablets contain Dihydrocodeine Tartrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dihydrocodeine tartrate, $C_{18}H_{23}NO_3,C_4H_6O_6$

95.0 to 105.0% of the stated amount.

Carry out the following procedures protected from light.

IDENTIFICATION

Mix a quantity of the powdered tablet containing 0.1 mg of Dihydrocodeine Tartrate and 4 mL of *water* with the aid of ultrasound and filter. Add 4 mL of *dichloromethane* and 0.5 mL of *strong sodium hydroxide solution* to the filtrate, mix and centrifuge. Isolate the lower layer and evaporate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of dihydrocodeine (*RS 102*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2 rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium if necessary, to produce a solution expected to contain 0.0033% w/v of Dihydrocodeine Tartrate.

www.webofpharma.com

https://thietbiuocngocanh.com/

(2) 0.0033% w/v of *dihydrocodeine tartrate BPCRS* in the dissolution medium.

(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5µm) (Hypersil Gold C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 284 nm.

(f) Inject 50 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of dihydrocodeine.

MOBILE PHASE

To 1.0 g of *sodium heptanesulfonate*, add 10.0 mL of *glacial acetic acid* and 4.0 mL of a solution of 5.0 mL of *triethylamine* diluted to 25.0 mL with a mixture of equal volumes of *acetonitrile* and *water*. Add 170 mL of *acetonitrile* and dilute to 1000 mL with *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retention of codeine with reference to dihydrocodeine (retention time about 11 minutes) is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{18}H_{23}NO_3,C_4H_6O_6$, in the medium from the chromatograms obtained and using the declared content of $C_{18}H_{23}NO_3,C_4H_6O_6$, in *dihydrocodeine tartrate BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a quantity of the powdered tablets containing 50 mg of Dihydrocodeine Tartrate and 25 mL of the mobile phase with the aid of ultrasound, dilute to 50 mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with an injection volume of 20 µL.

When the chromatograms are recorded under the prescribed conditions, the retention relative to dihydrocodeine (retention time about 11 minutes) of codeine is about 1.1.

www.webofpharma.com

https://thietbiuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to codeine is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%).

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dissolve a quantity of the powdered tablets containing 50 mg of Dihydrocodeine Tartrate and 25 mL of mobile phase with the aid of ultrasound, dilute to 50 mL with mobile phase. Dilute 1 volume to 10 volumes with mobile phase.
(2) 0.01% w/v of *dihydrocodeine tartrate BPCRS*.
(3) 0.04% w/v each of *dihydrocodeine tartrate BPCRS* and *codeine phosphate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but with an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dihydrocodeine and codeine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{23}NO_3,C_4H_6O_6$ in the tablets using the declared content of $C_{18}H_{23}NO_3,C_4H_6O_6$ in *dihydrocodeine tartrate BPCRS*.

STORAGE

Dihydrocodeine Tablets should be protected from light.

IMPURITIES

www.webofpharma.com

https://thietbiluocngocanh.com/

The impurities limited by the requirements of this monograph include those listed under Dihydrocodeine Tartrate.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

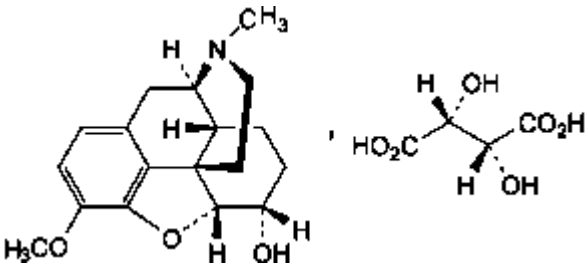
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Dihydrocodeine Tartrate

General Notices

(Dihydrocodeine Hydrogen Tartrate, Ph. Eur. monograph 1776)



$C_{22}H_{29}NO_9$ 451.5 *5965-13-9*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Co-dydramol Tablets

Dihydrocodeine Injection

Dihydrocodeine Oral Solution

Dihydrocodeine Tablets

Dihydrocodeine Prolonged-release Tablets

Ph Eur

DEFINITION

4,5α-Epoxy-3-methoxy-17-methylmorphinan-6α-ol hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of dihydrocodeine hydrogen tartrate*.

B. To about 0.1 g add 1 mL of *sulfuric acid R* and 0.05 mL of *ferric chloride solution R1* and heat on a water-bath. A brownish-yellow colour develops. Add 0.05 mL of *dilute nitric acid R*. The colour does not become red.

C. To 1 mL of solution S (see Tests) add 5 mL of *picric acid solution R*. Heat on a water-bath until a clear solution is obtained. Allow to cool. A precipitate is formed. Filter, wash with 5 mL of *water R* and dry at 100-105 °C. The crystals melt (2.2.14) at 220 °C to 223 °C.

D. It gives reaction (b) of tartrates (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

pH (2.2.3)

3.2 to 4.2 for solution S.

Specific optical rotation (2.2.7)

-70.5 to -73.5 (anhydrous substance).

Dilute 10.0 mL of solution S to 20.0 mL with *water R*.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of *codeine phosphate R* in 2.0 mL of the test solution and dilute to 25.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dilute 1.0 mL of the test solution to 200 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase To 1.0 g of *sodium heptanesulfonate R*, add 10.0 mL of *glacial acetic acid R* and 4.0 mL of a solution of 5.0 mL of *triethylamine R* diluted to 25.0 mL with a mixture of equal volumes of *water R* and *acetonitrile R*. Add 170 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 284 nm.

Injection 20 µL.

Run time 5 times the retention time of dihydrocodeine.

Retention time Dihydrocodeine = about 14 min.

System suitability Reference solution (a):

— *resolution*: minimum of 2 between the peaks due to dihydrocodeine and to impurity A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *any other peak*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent); disregard any peak due to tartaric acid (relative retention with reference to dihydrocodeine = about 0.25),

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.7 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

www.webofpharma.com

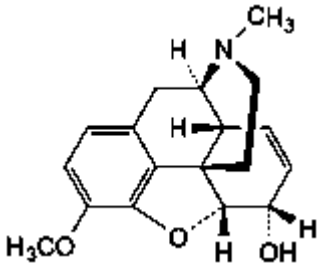
https://thuocngocanh.com/

1 mL of *0.1 M perchloric acid* is equivalent to 45.15 mg of $C_{22}H_{29}NO_9$.

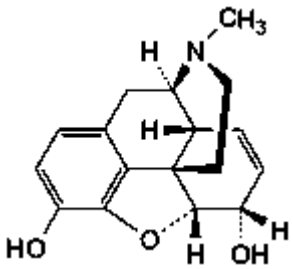
STORAGE

Protected from light.

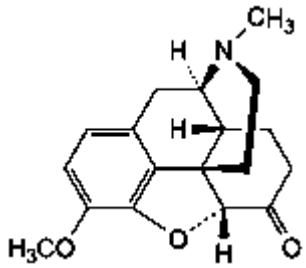
IMPURITIES



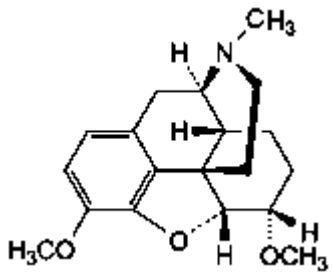
A. 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (codeine),



B. 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol (morphine),



C. 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (hydrocodone),



D. 4,5α-epoxy-3,6α-dimethoxy-17-methylmorphinan (tetrahydrothebaine).

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

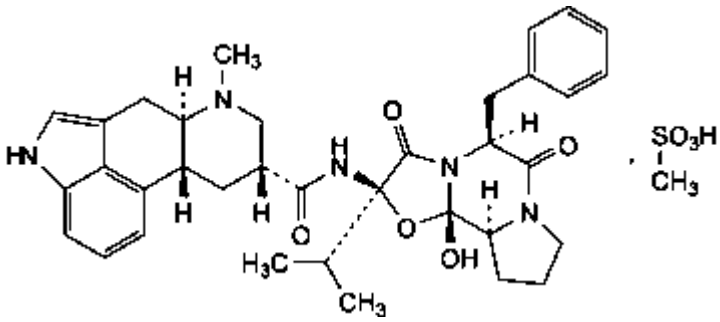
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dihydroergocristine Mesilate

General Notices

(Ph. Eur. monograph 1416)



$C_{36}H_{45}N_5O_8S$ 708 *24730-10-7*

Action and use

Vasodilator.

Ph Eur

DEFINITION

(6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxo-octahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulfonate.

Content

98.0 per cent to 102.0 per cent (dried substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in dihydroergocristine mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, fine crystalline powder.

Solubility

Slightly soluble in water, soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *dihydroergocristine mesilate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5 mL with the same mixture of solvents.

Reference solution Dissolve 0.10 g of *dihydroergocristine mesilate CRS* in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5 mL with the same mixture of solvents.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *dimethylformamide R*, *ether R* (2:15:85 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate protected from light.

Drying In a current of cold air for 5 min.

Detection Spray with *dimethylaminobenzaldehyde solution R7* and dry in a current of hot air for 2 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.20 g of the substance to be examined in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5 mL with the same mixture of solvents.

Reference solution Dissolve 0.20 g of *methanesulfonic acid R* in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5 mL with the same mixture of solvents. Dilute 1 mL of the solution to 10 mL with a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *concentrated ammonia R*, *butanol R*, *acetone R* (5:10:20:65 *V/V/V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Application 10 µL.

Development Over a path of 10 cm protected from light.

Drying In a current of cold air for not more than 1 min.

Detection Spray with a 1 g/L solution of *bromocresol purple R* in *methanol R*, adjusting the colour to violet-red with one drop of *dilute ammonia R1* and dry the plate in a current of hot air at 100 °C.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

Dissolve 0.50 g in *methanol R* and dilute to 25.0 mL with the same solvent.

pH (*2.2.3*)

4.0 to 5.0.

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-43 to -37 (dried substance).

Dissolve 0.250 g in *anhydrous pyridine R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test and preparation of the solutions protected from bright light.*

Test solution Dissolve 75.0 mg of the substance to be examined in 10 mL of *acetonitrile R*. Add 10 mL of a 1.0 g/L solution of *phosphoric acid R* and dilute to 50.0 mL with *water R*.

Reference solution Dissolve 20.0 mg of *codergocrine mesilate CRS* in 10 mL of *acetonitrile R*. Add 10 mL of a 1.0 g/L solution of *phosphoric acid R* and dilute to 50.0 mL with *water R*. Dilute 6.0 mL of the solution to 50.0 mL with a mixture of 20 volumes of *acetonitrile R*, 20 volumes of a 1.0 g/L solution of *phosphoric acid R* and 60 volumes of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: mix 100 volumes of *acetonitrile R* with 900 volumes of *water R* and add 10 volumes of *triethylamine R*;

— *mobile phase B*: mix 100 volumes of *water R* with 900 volumes of *acetonitrile R* and add 10 volumes of *triethylamine R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	75	25
5 - 20	75 → 25	25 → 75

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Relative retention With reference to dihydroergocristine (retention time = about 13.7 min): impurity F = about 0.8; impurity H = about 0.9; impurity I = about 1.02.

System suitability Reference solution:

— the chromatogram shows 4 peaks;

— *resolution*: minimum 1 between the peaks due to dihydroergocristine and impurity I.

Limits:

— *any impurity*: not more than the area of the peak due to dihydroergocristine in the chromatogram obtained with the reference solution (1 per cent);

— *total*: not more than twice the area of the peak due to dihydroergocristine in the chromatogram obtained with the reference solution (2 per cent);

— *disregard limit*: 0.1 times the area of the peak due to dihydroergocristine in the chromatogram obtained with the reference solution (0.1 per cent).

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 0.500 g by drying under high vacuum at 80 °C.

ASSAY

Dissolve 0.300 g in 60 mL of *pyridine R*. Pass a stream of *nitrogen R* over the surface of the solution and titrate with 0.1 M tetrabutylammonium hydroxide, determining the end-point potentiometrically (*2.2.20*). Note the volume used at the second point of inflexion.

www.webofpharma.com

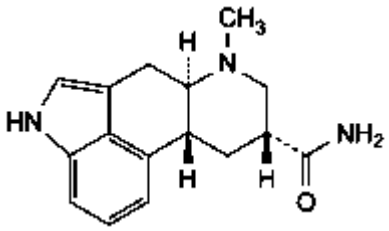
https://thuocngocanh.com/

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 35.39 mg of $C_{36}H_{45}N_5O_8S$.

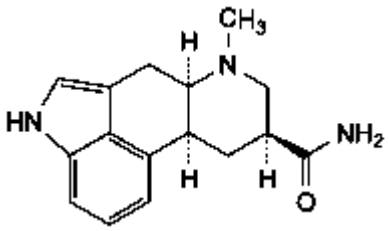
STORAGE

Store protected from light.

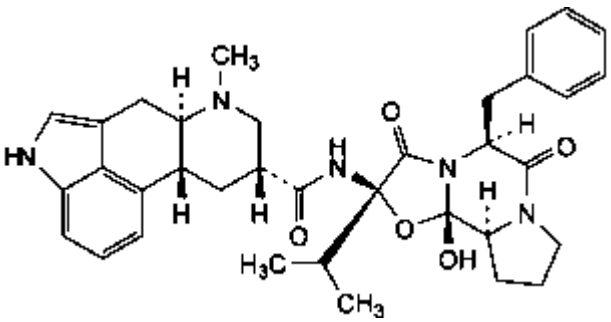
IMPURITIES



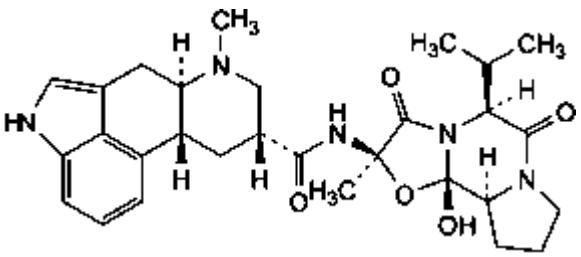
A. (6a*R*,9*R*,10a*R*)-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (6-methylergoline-8β-carboxamide),



B. (6a*R*,9*S*,10a*S*)-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (6-methylisoergoline-8α-carboxamide),



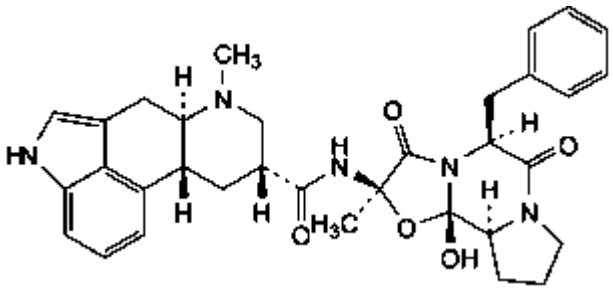
C. (6a*R*,9*R*,10a*R*)-*N*-[(2*S*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (2′-epidihydroergocristine),



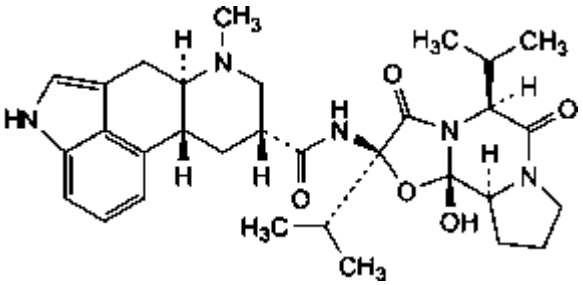
D. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-10b-hydroxy-2-methyl-5-(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergosine),

www.webofpharma.com

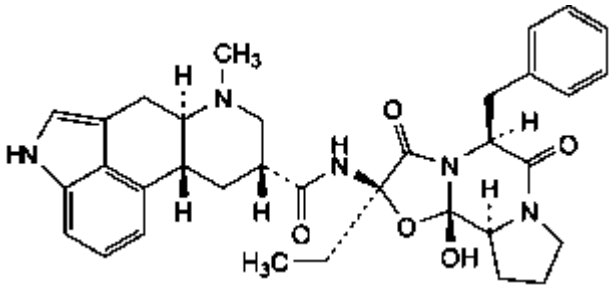
https://thuocngocanh.com/



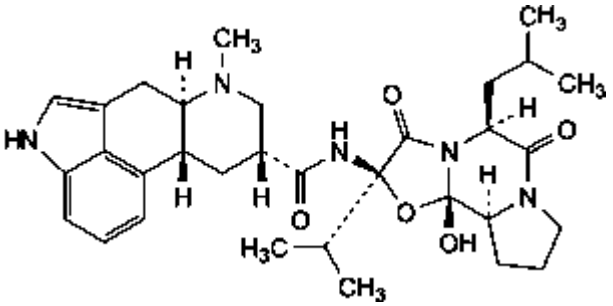
E. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline- 9-carboxamide (dihydroergotamine),



F. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)10b-hydroxy-2,5-bis(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergocornine),



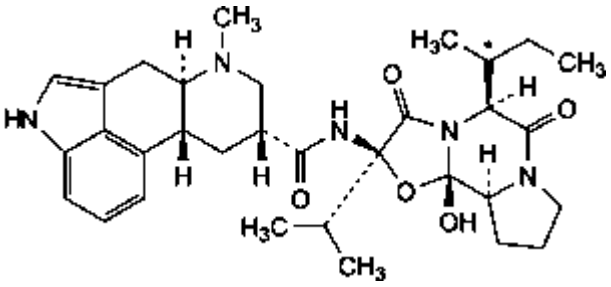
G. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-2-ethyl-10b-hydroxy-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergostine),



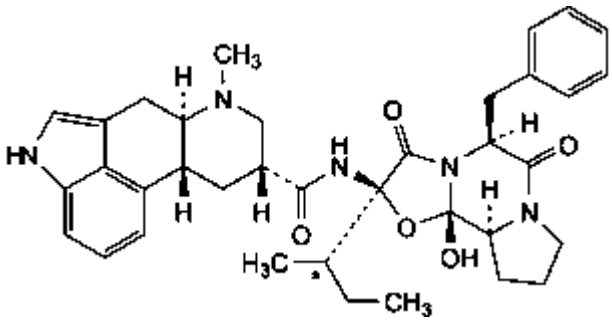
H. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-10b-hydroxy-2-(1-methylethyl)-5-(2-methylpropyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (α-dihydroergocryptine),

www.webofpharma.com

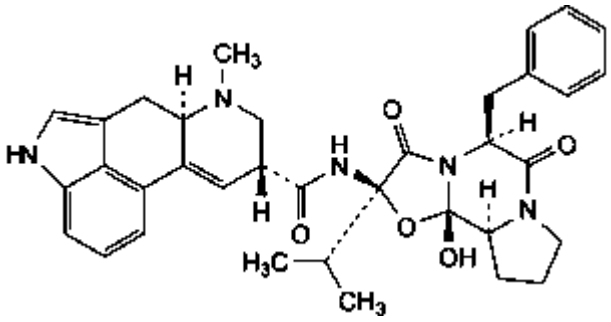
https://thuocngocanh.com/



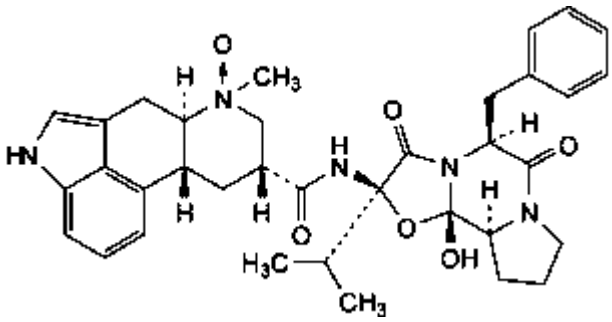
I. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-10b-hydroxy-2-(1-methylethyl)-5-[(1*RS*-1-methylpropyl]-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (β-dihydroergocryptine or epicriptine),



J. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-[(1*RS*)-1-methylpropyl]-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergosedmine),



K. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (ergocristine),



L. (6a*R*,7*RS*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide 7-oxide (dihydroergocristine 6-oxide).

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

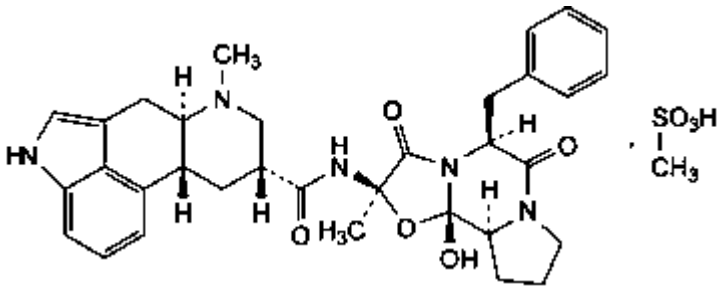
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Dihydroergotamine Mesilate

General Notices

(Ph. Eur. monograph 0551)



$C_{34}H_{41}N_5O_8S$ 680 *6190-39-2*

Action and use

Vasodilator.

Ph Eur

DEFINITION

(6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide methanesulfonate.

Content

98.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in dihydroergotamine mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 5.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent.

Spectral range 250-350 nm.

Absorption maxima 281 nm and 291 nm.

Shoulder 275 nm.

Absorbance Negligible above 320 nm.

Specific absorbance at the absorption maximum at 281 nm 95 to 105 (dried substance).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dihydroergotamine mesilate CRS*.

C. Thin-layer chromatography (2.2.27). *Prepare the reference solution and the test solution immediately before use.*

Solvent mixture *methanol R*, *methylene chloride R* (10:90 *V/V*).

Test solution Dissolve 5 mg of the substance to be examined in the solvent mixture and dilute to 2.5 mL with the solvent mixture.

Reference solution Dissolve 5 mg of *dihydroergotamine mesilate CRS* in the solvent mixture and dilute to 2.5 mL with the solvent mixture.

Plate *TLC silica gel G plate R*.

Mobile phase *concentrated ammonia R*, *methanol R*, *ethyl acetate R*, *methylene chloride R* (1:6:50:50 *V/V/V/V*).

Application 5 µL.

Development Protected from light, over a path of 15 cm; dry in a current of cold air for not longer than 1 min and repeat the development protected from light over a path of 15 cm using a freshly prepared amount of the mobile phase.

Drying In a current of cold air.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spray abundantly with *dimethylaminobenzaldehyde solution R7* and dry in a current of hot air for about 2 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. To 0.1 g of the substance to be examined, add 5 mL of *dilute hydrochloric acid R* and shake for about 5 min. Filter, then add 1 mL of *barium chloride solution R1*. The filtrate remains clear. Mix 0.1 g of the substance to be examined with 0.4 g of powdered *sodium hydroxide R*, heat to fusion and continue to heat for 1 min. Cool, add 5 mL of *water R*, boil and filter. Acidify the filtrate with *hydrochloric acid R1* and filter again. The filtrate gives reaction (a) of sulfates (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 or BY_7 (*2.2.2, Method II*).

Dissolve 0.10 g in a mixture of 0.1 mL of a 70 g/L solution of *methanesulfonic acid R* and 50 mL of *water R*.

pH (*2.2.3*)

4.4 to 5.4.

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-47 to -42 (dried substance).

Dissolve 0.250 g in *anhydrous pyridine R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 70 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 7 mg of the substance to be examined and 6.8 mg of *ergotamine tartrate CRS* (impurity A) (equivalent to 7 mg of ergotamine mesilate) in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 5 mL of this solution to 10 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *dihydroergotamine for peak identification CRS* (containing impurities A, B, C, D and E) in the solvent mixture, add 100 µL of *dilute sulfuric acid R* and dilute to 5 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: 3 g/L solution of *sodium heptanesulfonate monohydrate R* adjusted to pH 2.0 with *phosphoric acid R*;

— *mobile phase B*: mobile phase A, *acetonitrile for chromatography R* (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	58 → 40	42 → 60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with *dihydroergotamine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D and E.

Relative retention With reference to dihydroergotamine (retention time = about 6.5 min): impurity D = about 0.7; impurity C = about 0.86; impurity A = about 0.95; impurity B = about 1.2; impurity E = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity A and dihydroergotamine.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.3; impurity C = 1.3;

— *impurities B, E*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities A, D*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 4.0 per cent, determined on 0.500 g by drying at 105 °C *in vacuo* for 5 h.

ASSAY

Dissolve 0.500 g in a mixture of 10 mL of *anhydrous acetic acid R* and 70 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

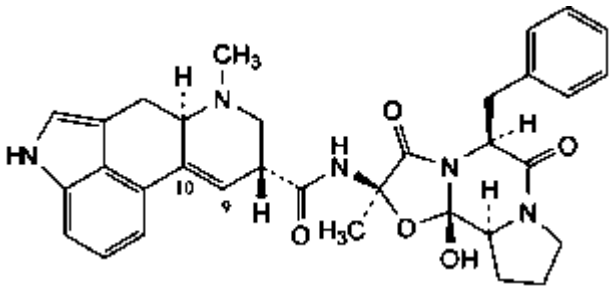
1 mL of *0.1 M perchloric acid* is equivalent to 68.00 mg of $C_{34}H_{41}N_5O_8S$.

STORAGE

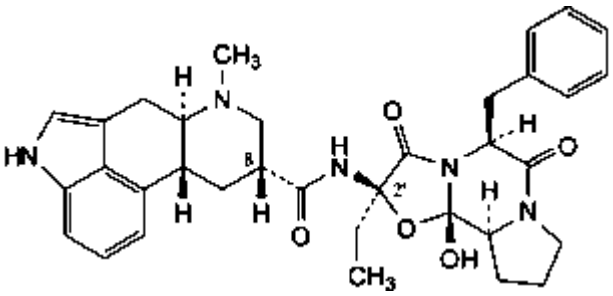
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*



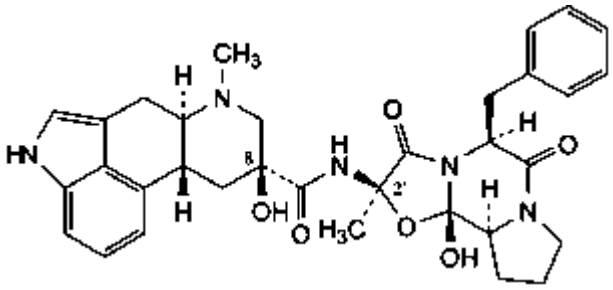
A. (6a*R*,9*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (ergotamine),



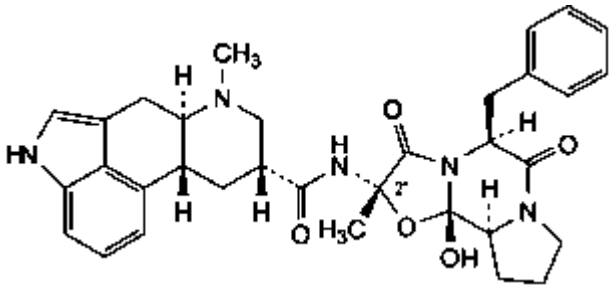
www.webofpharma.com

https://thuocngocanh.com/

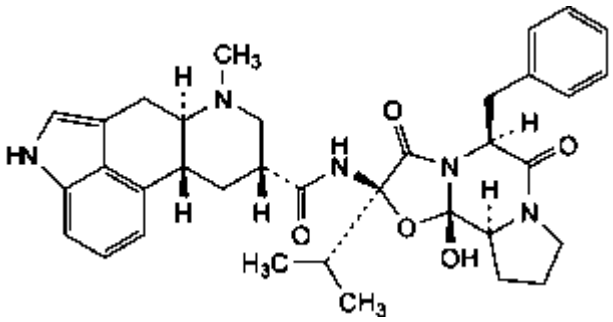
B. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-2-ethyl-10b-hydroxy-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (9,10-dihydroergostine),



C. (6a*R*,9*S*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-9-hydroxy-7-methyl-4,6,6a,7,8,9,10,10aoctahydroindolo[4,3-*fg*]quinoline-9-carboxamide (8-hydroxy-9,10-dihydroergotamine),



D. (6a*R*,9*R*,10a*R*)-*N*-[(2*S*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10aoctahydroindolo[4,3-*fg*]quinoline-9-carboxamide (2′-*epi*-9,10-dihydroergotamine),



E. (6a*R*,9*R*,10a*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-(1-methylethyl)-3,6-dioxo-octahydro-8*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide (dihydroergocristine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

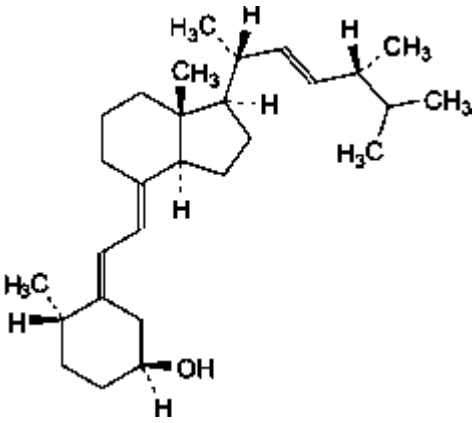
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dihydrotachysterol

General Notices

(Ph. Eur. monograph 2014)



$C_{28}H_{46}O$ 398.7 *67-96-9*

Action and use

Vitamin D analogue.

Ph Eur

DEFINITION

(5*E*,7*E*,22*E*)-9,10-Seco-10α-ergosta-5,7,22-trien-3β-ol.

Content

97.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

Colourless crystals or white or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in hexane, sparingly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *dihydrotachysterol CRS*.

If the spectra obtained in the solid state show differences, record new spectra using the residues after recrystallisation from *methanol R*.

TESTS

Specific optical rotation (2.2.7)

+ 99 to + 103.

Dissolve 0.500 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 10.00 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 1.0 mg of *dihydrotachysterol for system suitability CRS* (containing impurities A, B and C) in *acetonitrile R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 10.00 mg of *dihydrotachysterol CRS* in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (c) Dilute 5.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 5.0 mL of this solution to 50.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.25 m, Ø = 3.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography for separation of polycyclic aromatic hydrocarbons R* (3 µm);

— *temperature*: 40 °C.

Mobile phase *decanol R*, *water for chromatography R*, *acetonitrile R1* (1:25:1000 *V/V/V*).

Flow rate 0.5 mL/min.

Detection Variable-wavelength spectrophotometer capable of operating at 251 nm and at 203 nm.

Injection 5 µL of the test solution and reference solutions (a) and (c).

Run time Twice the retention time of dihydrotachysterol.

Identification of impurities Reference solution (a):

www.webofpharma.com

https://thuocngocanh.com/

— use the chromatogram obtained at 203 nm and the chromatogram obtained at 203 nm supplied with *dihydrotachysterol for system suitability CRS* to identify the peak due to impurity A;

— use the chromatogram obtained at 251 nm and the chromatogram obtained at 251 nm supplied with *dihydrotachysterol for system suitability CRS* to identify the peaks due to impurities B and C.

Relative retention With reference to dihydrotachysterol (retention time = about 15 min): impurity B = about 0.9; impurity C = about 1.2; impurity A (not visible at 251 nm, detected at 203 nm) = about 1.2.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to dihydrotachysterol in the chromatogram obtained at 251 nm.

Examine the chromatogram obtained at 203 nm for impurity A and the chromatogram obtained at 251 nm for impurities other than A.

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurities B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *total (including A)*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) at 251 nm (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (*2.5.32*)

Maximum 0.10 per cent, determined on 40.0 mg.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 251 nm.

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{28}H_{46}O$ taking into account the assigned content of *dihydrotachysterol CRS*.

STORAGE

www.webofpharma.com

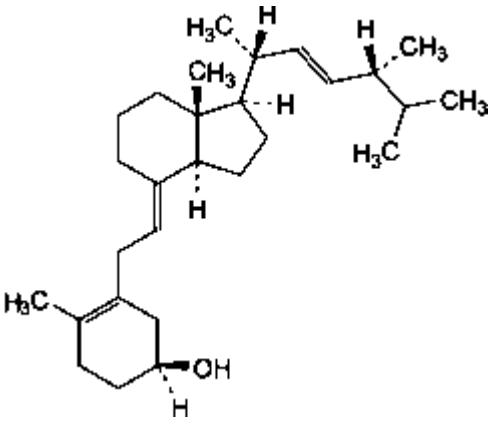
https://thuocngocanh.com/

Under an inert gas, in an airtight container, at a temperature of 2 °C to 8 °C.

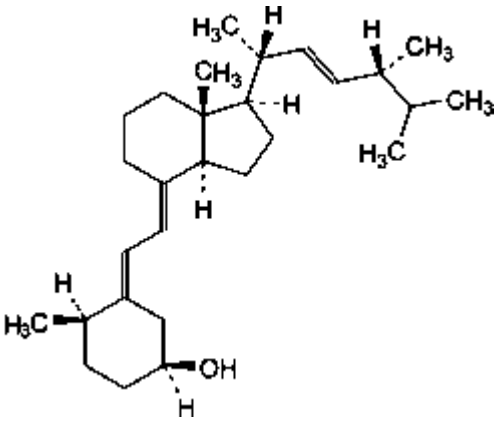
The contents of an opened container are to be used immediately.

IMPURITIES

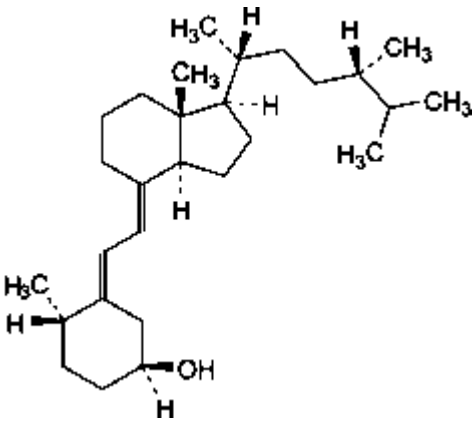
Specified impurities *A, B, C.*



A. (7*E*,22*E*)-9,10-secoergosta-5(10),7,22-trien-3β-ol (dihydrovitamin D_2-I),



B. (5*E*,7*E*,22*E*)-9,10-secoergosta-5,7,22-trien-3β-ol (dihydrovitamin D_2-IV),



C. (5*E*,7*E*)-9,10-seco-10α-ergosta-5,7-dien-3β-ol (dihydrotachysterol$_4$).

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

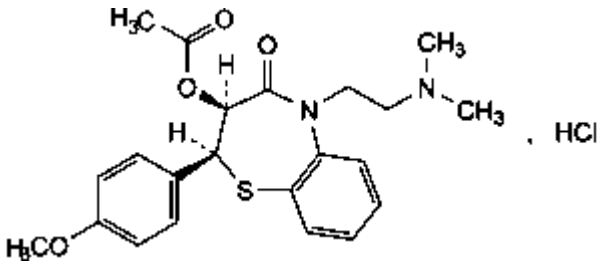
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diltiazem Hydrochloride

General Notices

(Ph. Eur. monograph 1004)



$C_{22}H_{27}ClN_2O_4S$ 451.0 *33286-22-5*

Action and use

Calcium channel blocker.

Preparations

Diltiazem Oral Suspension

Diltiazem Prolonged-release Tablets

Ph Eur

DEFINITION

Hydrochloride of (2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, in methanol and in methylene chloride, slightly soluble in anhydrous ethanol.

www.webofpharma.com

https://thuocngocanh.com/

mp

About 213 °C, with decomposition.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *diltiazem hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methylene chloride R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 50 mg of *diltiazem hydrochloride CRS* in *methylene chloride R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *acetic acid R*, *water R*, *methylene chloride R*, *anhydrous ethanol R* (1:3:10:12 *V/V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 50 mg in 5 mL of *water R*. Add 1 mL of *ammonium reineckate solution R*. A pink precipitate is produced.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

4.3 to 5.3.

www.webofpharma.com

https://thuocngocanh.com/

Dilute 2.0 mL of solution S to 10.0 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

+ 115 to + 120 (dried substance).

Dilute 5.0 mL of solution S to 25.0 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 200.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *diltiazem for system suitability CRS* (containing impurity A) in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *diltiazem impurity F CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Mix 5 volumes of *anhydrous ethanol R*, 25 volumes of *acetonitrile R* and 70 volumes of a solution containing 6.8 g/L of *potassium dihydrogen phosphate R* and 0.1 mL/L of *N,N-dimethyloctylamine R*, adjusted to pH 4.5 with *dilute phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL.

Run time 5 times the retention time of diltiazem.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity F.

Relative retention With reference to diltiazem (retention time = about 5 min): impurity F = about 0.5; impurity A = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity A and diltiazem;

— *symmetry factor*: maximum 2.0 for the peak due to impurity A; if necessary, adjust the concentration of *N,N*-dimethyloctylamine in the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurity F*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in a mixture of 2 mL of *anhydrous formic acid R* and 60 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 45.1 mg of $C_{22}H_{27}ClN_2O_4S$.

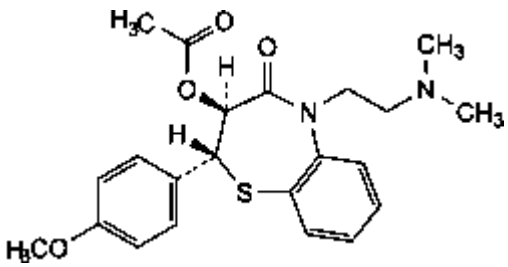
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *F.*

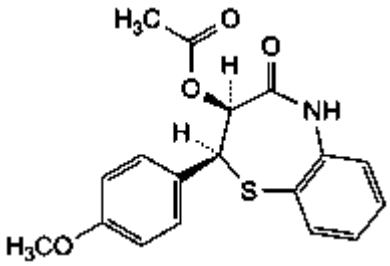
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E.*



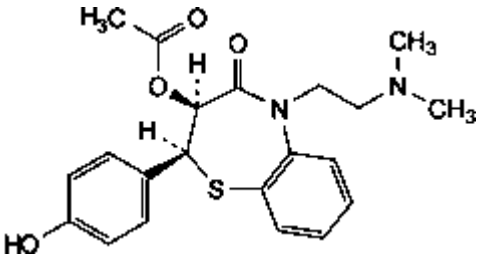
www.webofpharma.com

https://thuocngocanh.com/

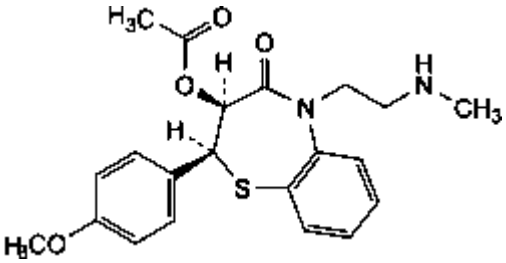
A. (2*R*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



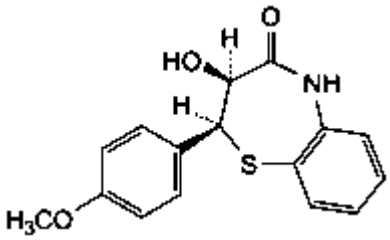
B. (2*S*,3*S*)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



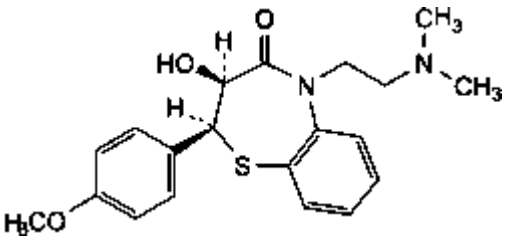
C. (2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-2-(4-hydroxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



D. (2*S*,3*S*)-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate,



E. (2*S*,3*S*)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one,



F. (2*S*,3*S*)-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diltiazem Oral Suspension

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Calcium channel blocker.

DEFINITION

Diltiazem Oral Suspension is a suspension of Diltiazem Hydrochloride in a suitable flavoured vehicle.

The oral suspension with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of diltiazem hydrochloride, $C_{22}H_{26}N_2O_4S,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *dichloromethane*.

(1) Dilute a quantity of the oral suspension containing 50 mg of Diltiazem Hydrochloride to 25 mL, shake, allow the layers to separate, centrifuge an aliquot of the lower layer and use the lower layer.

(2) 0.2% w/v of *diltiazem hydrochloride BPCRS*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 5M *acetic acid*, 6 volumes of *water*, 20 volumes of *dichloromethane* and 24 volumes of *absolute ethanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single compact spot.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.7 to 4.7, Appendix V L.

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase immediately before use.

(1) Shake a weighed quantity of the oral suspension containing 12 mg of Diltiazem Hydrochloride in 70 mL for 30 minutes, dilute to 100 mL and filter (a 0.45-µm PTFE filter is suitable).

(2) 0.012% w/v of *diltiazem hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

25 volumes of a 0.116% w/v solution of (1*S*)-(+)-*10-camphorsulfonic acid* in 0.1M *sodium acetate*, previously adjusted to pH 6.2 with 0.1M *sodium hydroxide*, 25 volumes of *methanol* and 50 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the Oral Suspension, Appendix V G, and calculate the content of $C_{22}H_{26}N_2O_4S$,HCl, weight in volume, using the declared content of $C_{22}H_{26}N_2O_4S$,HCl in *diltiazem hydrochloride BPCRS*.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Diltiazem Oral Suspension should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diltiazem Prolonged-release Tablets

General Notices

Prolonged-release Diltiazem Tablets

Diltiazem Prolonged-release Tablets from different manufacturers containing more than 60 mg of Diltiazem Hydrochloride, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Calcium channel blocker.

DEFINITION

Diltiazem Prolonged-release Tablets contain Diltiazem Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Diltiazem Hydrochloride. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diltiazem hydrochloride, $C_{22}H_{26}N_2O_4S,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 50 mg of Diltiazem Hydrochloride with 25 mL of *methanol* for 15 minutes and filter through a 0.45-µm PTFE filter.

(2) 0.2% w/v of *diltiazem hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel F_{254}* precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

1 volume of 5M *acetic acid*, 3 volumes of *water*, 10 volumes of *dichloromethane* and 12 volumes of *absolute ethanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (50%)* prepared immediately before use.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.12 g of Diltiazem Hydrochloride with 70 mL, dilute to 100 mL and filter through a 0.45-µm PTFE filter. Dilute 1 volume of the resulting solution to 5 volumes.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.024% w/v of *diltiazem impurity standard BPCRS*.
(4) 0.00024% w/v of *diltiazem impurity F EPCRS*.
(5) Dilute 1 volume of solution (2) to 10 volumes..

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 5 times the retention time of diltiazem.

MOBILE PHASE

5 volumes of *absolute ethanol*, 25 volumes of *acetonitrile* and 70 volumes of a phosphate buffer prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* in 250 mL of *water*, adding 0.1 mL of N,N-*dimethyloctylamine* and sufficient *water* to produce 1000 mL and adjusting the pH to 4.5 with 2M *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to diltiazem impurity A and diltiazem is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuathuocngocanh.com/

the area of any peak corresponding to impurity F is not greater than the corresponding peak obtained in the chromatogram obtained with solution (4) (1.0%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *methanol (50%)* immediately before use.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 50 mg of Diltiazem Hydrochloride with 70 mL for 20 minutes, cool to room temperature, dilute to 100 mL and filter through a 0.45-µm PTFE filter. Dilute 1 volume of the resulting filtrate to 5 volumes.

(2) 0.01% w/v of *diltiazem hydrochloride BPCRS*.

(3) 0.01% w/v of *diltiazem impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to diltiazem impurity A and diltiazem is at least 4.0.

If necessary, adjust the concentration of *N*,*N*-dimethyloctylamine in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{26}N_2O_4S,HCl$ in the tablets using the declared content of $C_{22}H_{26}N_2O_4S,HCl$ in *diltiazem hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those impurities listed under Diltiazem Hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

https://thuathuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dilute Adrenaline Injection 1 in 10,000/Dilute Epinephrine Injection 1 in 10,000

General Notices

Action and use

Adrenoceptor agonist.

DEFINITION

Dilute Adrenaline Injection 1 in 10,000 is a sterile, isotonic solution containing either 0.018% w/v of Adrenaline Acid Tartrate or 0.01% w/v of Adrenaline in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of adrenaline, $C_9H_{13}NO_3$

0.00900 to 0.01150% w/v, of which at least 0.00850% w/v is L-adrenaline.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. To 10 mL of the injection add 2 mL of a 10% w/v solution of *disodium hydrogen orthophosphate* and sufficient *iodinated potassium iodide solution* to produce a brown colour. Remove excess iodine by adding 0.1M *sodium thiosulfate* drop wise. A red or pink colour is produced.

TESTS

Acidity

pH, 2.8 to 4.0, Appendix V L.

Related substances

The total of all impurities from methods A and B is not more than 19.0%.

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. Prepare the solutions immediately before use and protect from light. Store and inject the solutions at 4°, using a cooled autosampler.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dilute the injection to produce a solution containing the equivalent of 0.005% w/v of Adrenaline.

(2) Dilute 3 volumes of solution (1) to 20 volumes.

(3) 0.005% w/v of *(±)-adrenaline hydrochloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *β-cyclodextrin hydroxypropyl ether derivative for chiral chromatography* (3 µm) (ORpak CDBS-453 Chiral is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use a column temperature of 10°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of a solution containing 0.2M *potassium chloride* and 0.4% v/v of *glacial acetic acid*, 3 volumes of *acetonitrile* and 96 volumes of 0.2M *potassium chloride*.

When the chromatograms are recorded under the prescribed conditions, the retention time of D-adrenaline (impurity 1) relative to L-adrenaline (retention time about 13 minutes) is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks in the chromatogram is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to D-adrenaline (impurity 1) is not greater than the sum of the areas of the peaks due to L-adrenaline and D-adrenaline in the chromatogram obtained with solution (2) (15%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared protected from light.

(1) The preparation being examined.

(2) Dilute 1 volume of solution (1) to 10 volumes with the mobile phase.

(3) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

(4) 0.01% w/v of *adrenaline impurity standard BPCRS* in the mobile phase.

(5) Dilute 1 volume of solution (3) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Eclipse Plus C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of adrenaline.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of a solution containing 0.2mM *disodium edetate*, 5.4mM *sodium heptanesulfonate monohydrate* and 23mM *tetramethylammonium hydrogen sulfate*, adjusted to pH 3.5 with 1M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions the retentions relative to adrenaline (retention time about 18 minutes) are: impurity F, about 0.1; impurity 2, about 0.2; impurity B, about 0.6 and impurity C, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity F and impurity 2 is at least 10.0.

LIMITS

Identify any peaks corresponding to impurities F, 2 and C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of these peaks by the following correction factors: impurity F, 1.3; impurity 2, 0.7 and impurity C, 0.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than 1.8 times the area of the principal peak in the chromatogram obtained with solution (2) (18%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the sum of the areas of any *secondary peaks*, excluding any peak corresponding to impurity F, is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase, prepared protected from light.

(1) The preparation being examined.

(2) 0.02% w/v of *adrenaline acid tartrate BPCRS*.

(3) 0.02% w/v of *adrenaline acid tartrate BPCRS* and 0.02% w/v of *noradrenaline acid tartrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

www.webofpharma.com

https://thietkeuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *methanol R1* and 95 volumes of a solution containing 0.2mM *disodium edetate*, 5.4mM *sodium heptanesulfonate monohydrate* and 23mM *tetramethylammonium hydrogen sulfate*, adjusted to pH 3.5 with 1M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{13}NO_3$ in the injection using the declared content of $C_9H_{13}NO_3$ in *adrenaline acid tartrate BPCRS*.

Calculate the L-adrenaline content using the following equation:

$$C_{LA} = C_A \times \left(\frac{PA_{LA}}{PA_A} \right)$$

where:

C_{LA} = content of L-adrenaline in % w/v

C_A = content of $C_9H_{13}NO_3$ in % w/v, determined in the Assay

PA_{LA} = the area of the peak corresponding to L-adrenaline in the chromatogram obtained with solution (1) of Related substances test A

PA_A = the sum of the areas of the peaks corresponding to L-adrenaline and D-adrenaline in the chromatogram obtained with solution (1) of Related substances test A

STORAGE

Dilute Adrenaline Injection 1 in 10,000 should be protected from light and stored at a temperature not exceeding 25°.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of adrenaline (epinephrine).

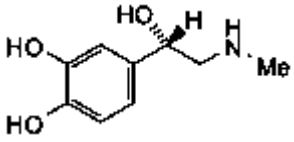
Dilute Adrenaline Injection contains the equivalent of adrenaline (epinephrine), 1 in 10,000 (100 µg in 1 mL).

IMPURITIES

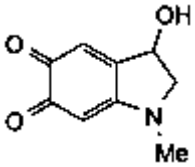
www.webofpharma.com

https://thietbiuocngocanh.com/

The impurities limited by the requirements of this monograph include impurities B and C listed under Adrenaline Acid Tartrate/Epinephrine Acid Tartrate, impurity F listed under Adrenaline/Epinephrine and:



1. (1*S*)-1-(3,4-dihydroxyphenyl)-2-(methylamino)ethan-1-ol (D-adrenaline)



2. 3-hydroxy-2,3-dihydro1*H*-indole-5,6-dione (adrenochrome)

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dilute Ammonia Solution

General Notices

DEFINITION

Dilute Ammonia Solution contains 10% w/w of ammonia. It is prepared by diluting Strong Ammonia Solution with freshly boiled and cooled Purified Water.

Content of ammonia, NH_3

9.5 to 10.5% w/w.

TESTS

Relative density

0.958 to 0.962, Appendix V G.

ASSAY

Weigh 6 g into 50 mL of *1M hydrochloric acid VS* and titrate the excess of acid with *1M sodium hydroxide VS* using *methyl red solution* as indicator. Each mL of *1M hydrochloric acid VS* is equivalent to 17.03 mg of NH_3.

When ammonia solution is prescribed or demanded, Dilute Ammonia Solution shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dilute Ethanols

General Notices

DEFINITION

The official Dilute Ethanols contain 90, 80, 70, 60, 50, 45, 25 and 20% v/v respectively of ethanol. They may be prepared as described below, the final adjustment of volume being made at the same temperature, 20°, as that at which the Ethanol (96 per cent) is measured.

NOTE *On mixing ethanol and water, contraction of volume and rise of temperature occur*.

TESTS

Acidity or alkalinity; Appearance; Volatile impurities; Residue on evaporation

Comply with the requirements stated under Ethanol (96 per cent).

ETHANOL (90 PER CENT)

Alcohol (90 per cent); Rectified Spirit

Dilute 934 ml of Ethanol (96 per cent) to 1000 ml with Purified Water.

Content of ethanol

89.6 to 90.5% v/v.

Apparent density

826.4 to 829.4 kg m^{-3}, Appendix V G.

ETHANOL (80 PER CENT)

Alcohol (80 per cent)

Dilute 831 ml of Ethanol (96 per cent) to 1000 ml with Purified Water.

Content of ethanol

79.5 to 80.3% v/v.

Apparent density

857.4 to 859.6 kg m^{-3}, Appendix V G.

ETHANOL (70 PER CENT)

www.webofpharma.com

https://thuocngocanh.com/

Alcohol (70 per cent)

Dilute 727 ml of Ethanol (96 per cent) to 1000 ml with Purified Water.

Content of ethanol

69.5 to 70.4% v/v.

Apparent density

883.5 to 885.8 kg m^{-3}, Appendix V G.

ETHANOL (60 PER CENT)

Alcohol (60 per cent)

Dilute 623 ml of Ethanol (96 per cent) to 1000 ml with Purified Water.

Content of ethanol

59.7 to 60.2% v/v.

Apparent density

907.6 to 908.7 kg m^{-3}, Appendix V G.

ETHANOL (50 PER CENT)

Alcohol (50 per cent)

Dilute 519 ml of Ethanol (96 per cent) to 1000 ml with Purified Water.

Content of ethanol

49.6 to 50.2% v/v.

Apparent density

928.6 to 929.8 kg m^{-3}, Appendix V G.

ETHANOL (45 PER CENT)

Alcohol (45 per cent)

Dilute 468 ml of Ethanol (96 per cent) to 1000 ml with Purified Water.

Content of ethanol

44.7 to 45.3% v/v.

www.webofpharma.com

https://thietbiuocngocanh.com/

Apparent density

938.0 to 939.0 kg m^{-3}, Appendix V G.

ETHANOL (25 PER CENT)

Alcohol (25 per cent)

Dilute 259 ml of Ethanol (96 per cent) to 1000 ml with Purified Water.

Content of ethanol

24.6 to 25.4% v/v.

Apparent density

966.6 to 967.5 kg m^{-3}, Appendix V G.

ETHANOL (20 PER CENT)

Alcohol (20 per cent)

Dilute 207 ml of Ethanol (96 per cent) to 1000 ml with Purified Water.

Content of ethanol

19.5 to 20.5% v/v.

Apparent density

972.0 to 973.1 kg m^{-3}, Appendix V G.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dilute Hydrochloric Acid

General Notices

(Ph. Eur. monograph 0003)

Ph Eur

DEFINITION

Content

9.5 per cent *m/m* to 10.5 per cent *m/m* of HCl (M_r 36.46).

PREPARATION

To 726 g of *water R* add 274 g of concentrated hydrochloric acid and mix.

IDENTIFICATION

A. It is strongly acid (*2.2.4*).

B. It gives reaction (a) of chlorides (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

Appearance

It is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Free chlorine

Maximum 1 ppm.

To 60 mL add 50 mL of *carbon dioxide-free water R*, 1 mL of a 100 g/L solution of *potassium iodide R* and 0.5 mL of *iodide-free starch solution R*. Allow to stand in the dark for 2 min. Any blue colour disappears on the addition of 0.2 mL of *0.01 M sodium thiosulfate*.

Sulfates (*2.4.13*)

Maximum 5 ppm.

To 26 mL add 10 mg of *sodium hydrogen carbonate R* and evaporate to dryness on a water-bath. Dissolve the residue in 15 mL of *distilled water R*.

Residue on evaporation

www.webofpharma.com

https://thietbiuocngocanh.com/

Maximum 0.01 per cent.

Evaporate 100.0 g to dryness on a water-bath or using a rotary evaporator and dry the residue at 100-105 °C. The residue weighs a maximum of 10 mg.

ASSAY

To 6.00 g add 30 mL of *water R*. Titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

1 mL of *1 M sodium hydroxide* is equivalent to 36.46 mg of HCl.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dilute Phosphoric Acid

General Notices

(Ph. Eur. monograph 0005)

Ph Eur

DEFINITION

Content

9.5 per cent *m/m* to 10.5 per cent *m/m* of H_3PO_4 (M_r 98.0).

PREPARATION

To 885 g of *water R* add 115 g of concentrated phosphoric acid and mix.

IDENTIFICATION

A. It is strongly acid (*2.2.4*).

B. Solution S (see Tests), neutralised with *dilute sodium hydroxide solution R*, gives the reactions of phosphates (*2.3.1*).

TESTS

Solution S

Dilute 86 g to 150 mL with *water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Substances precipitated with ammonia

To 10 mL of solution S add 8 mL of *dilute ammonia R1*. Any opalescence in the solution is not more intense than that in a mixture of 10 mL of solution S and 8 mL of *water R*.

Hypophosphorous acid and phosphorous acid

To 5 mL of solution S add 2 mL of *silver nitrate solution R2* and heat on a water-bath for 5 min. The solution shows no change in appearance.

Chlorides (*2.4.4*)

www.webofpharma.com

https://thietbiuocngocanh.com/

Maximum 6 ppm, determined on solution S.

Sulfates (*2.4.13*)

Maximum 10 ppm, determined on the preparation to be examined.

Iron (*2.4.9*)

Maximum 6 ppm.

Dilute 3 mL of solution S to 10 mL with *water R*.

ASSAY

Dilute 4.30 g in 30 mL of *water R*. Titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added at the 2nd inflexion point.

1 mL of *1 M sodium hydroxide* is equivalent to 49.00 mg of H_3PO_4.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thastuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dilute Sodium Hypochlorite Solution

General Notices

Dilute Sodium Hypochlorite Cutaneous Solution

DEFINITION

Dilute Sodium Hypochlorite Solution is an aqueous *cutaneous solution* of sodium hypochlorite containing 1% of available chlorine. It may contain suitable stabilising agents and Sodium Chloride.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of available chlorine, Cl

0.90 to 1.10% w/w.

ASSAY

Add 10 mL of the solution to a mixture of 50 mL of *water*, 1 g of *potassium iodide* and 12.5 mL of 2M *acetic acid*. Titrate with 0.1M *sodium thiosulfate VS* using *starch solution* as indicator. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 3.545 mg of Cl. Determine the *weight per mL* of the solution, Appendix V G, and calculate the percentage w/w of available chlorine.

STORAGE

Dilute Sodium Hypochlorite Solution should be kept in a well-filled container and protected from light. It should be stored at a temperature not exceeding 20° and away from acids.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dilute Sulfuric Acid

General Notices

Dilute Sulphuric Acid

DEFINITION

Dilute Sulfuric Acid is prepared by adding 104 g of Sulfuric Acid to 896 g of Purified Water with constant stirring and cooling. It contains not less than 9.5% and not more than 10.5% w/w of H_2SO_4.

Weight per mL

1.062 g to 1.072 g, Appendix V G.

ASSAY

To 10 g add 40 mL of *water* and titrate with *1M sodium hydroxide VS* using *methyl orange solution* as indicator. Each mL of *1M sodium hydroxide VS* is equivalent to 49.04 mg of H_2SO_4.

© Crown Copyright 2022

www.webofpharma.com

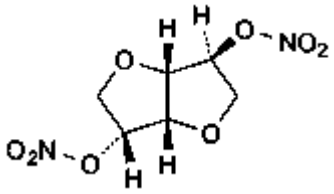
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diluted Isosorbide Dinitrate

General Notices

(Ph. Eur. monograph 1117)



$C_6H_8N_2O_8$ 236.1

Action and use

Nitric acid analogue; treatment of angina pectoris.

Preparation

Isosorbide Dinitrate Tablets

Ph Eur

DEFINITION

Dry mixture of isosorbide dinitrate and *Lactose monohydrate (0187)* or *Mannitol (0559)*.

Content

95.0 per cent *m/m* to 105.0 per cent *m/m* of the content of 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate stated on the label.

CAUTION: undiluted isosorbide dinitrate may explode if subjected to percussion or excessive heat. Appropriate precautions must be taken and only very small quantities handled.

CHARACTERS

Appearance

Undiluted isosorbide dinitrate is a fine, white or almost white, crystalline powder.

Solubility

Undiluted isosorbide dinitrate is very slightly soluble in water, very soluble in acetone, sparingly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

The solubility of the diluted product depends on the diluent and its concentration.

IDENTIFICATION

First identification: A, C, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs prepared with the residue obtained in identification test D.

Comparison *isosorbide dinitrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Shake a quantity of the substance to be examined corresponding to 10 mg of isosorbide dinitrate with 10 mL of *ethanol (96 per cent) R* for 5 min and filter.

Reference solution Shake a quantity of *isosorbide dinitrate CRS* corresponding to 10 mg of isosorbide dinitrate with 10 mL of *ethanol (96 per cent) R* for 5 min and filter.

Plate *TLC silica gel G plate R*.

Mobile phase *methanol R*, *methylene chloride R* (5:95 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In a current of air.

Detection Spray with freshly prepared *potassium iodide and starch solution R*; expose to ultraviolet light at 254 nm for 15 min and examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Thin-layer chromatography (2.2.27).

Test solution Shake a quantity of the substance to be examined corresponding to 0.10 g of lactose or mannitol with 10 mL of *water R*. Filter if necessary.

Reference solution (a) Dissolve 0.10 g of *lactose monohydrate R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 0.10 g of *mannitol R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (c) Mix equal volumes of reference solutions (a) and (b).

Plate *TLC silica gel G plate R*.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase *water R*, *methanol R*, *anhydrous acetic acid R*, *ethylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately since a slight excess of water produces cloudiness.

Application 1 µL; thoroughly dry the points of application.

Development A Over a path of 15 cm.

Drying A In a current of warm air.

Development B Immediately, over a path of 15 cm, after renewing the mobile phase.

Drying B In a current of warm air.

Detection Spray with *4-aminobenzoic acid solution R*, dry in a current of cold air until the acetone is removed, then heat at 100 °C for 15 min; allow to cool, spray with a 2 g/L solution of *sodium periodate R*, dry in a current of cold air, and heat at 100 °C for 15 min.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a) for lactose or to the principal spot in the chromatogram obtained with reference solution (b) for mannitol.

D. Shake a quantity of the substance to be examined corresponding to 25 mg of isosorbide dinitrate with 10 mL of *acetone R* for 5 min. Filter, evaporate to dryness at a temperature below 40 °C and dry the residue over *diphosphorus pentoxide R* at a pressure of 0.7 kPa for 16 h. The melting point (*2.2.14*) of the residue is 69 °C to 72 °C.

TESTS

Impurity A

Thin-layer chromatography (*2.2.27*).

Test solution Shake a quantity of the substance to be examined corresponding to 0.10 g of isosorbide dinitrate with 5 mL of *ethanol (96 per cent) R* and filter.

Reference solution Dissolve 10 mg of *potassium nitrate R* in 1 mL of *water R* and dilute to 100 mL with *ethanol (96 per cent) R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *toluene R* (15:30:60 *V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In a current of air until the acetic acid is completely removed.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spray copiously with freshly prepared *potassium iodide and starch solution R*; expose to ultraviolet light at 254 nm for 15 min and examine in daylight.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the principal spot in the chromatogram obtained with the reference solution (0.5 per cent, calculated as potassium nitrate).

Impurities B and C

Liquid chromatography (*2.2.29*).

Test solution (a) Sonicate a quantity of the substance to be examined corresponding to 25.0 mg of isosorbide dinitrate with 20 mL of the mobile phase for 15 min and dilute to 25.0 mL with the mobile phase. Filter the solution through a suitable membrane filter.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Sonicate a quantity of *isosorbide dinitrate CRS* corresponding to 25.0 mg of isosorbide dinitrate with 20 mL of the mobile phase for 15 min and dilute to 25.0 mL with the mobile phase. Filter the solution through a suitable membrane filter.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 10.0 mg of *isosorbide-2-nitrate CRS* (impurity B) in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 0.1 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (d) Dissolve 10.0 mg of *isosorbide mononitrate CRS* (impurity C) in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 0.1 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (e) Dissolve 5 mg of *isosorbide-2-nitrate CRS* (impurity B) in the mobile phase and dilute to 10 mL with the mobile phase. To 1 mL of this solution add 0.5 mL of reference solution (a) and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (10 µm).

Mobile phase *anhydrous ethanol R*, *trimethylpentane R* (15:85 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 210-215 nm.

Injection 10 µL of test solution (a) and reference solutions (c), (d) and (e).

Retention time Isosorbide dinitrate = about 5 min; impurity B = about 8 min; impurity C = about 11 min.

System suitability Reference solution (e):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 6.0 between the peaks due to isosorbide dinitrate and impurity B.

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent).

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for impurities B and C with the following modifications.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (b) and reference solution (b).

If the areas of the peaks from 2 successive injections of reference solution (b) do not agree to within 1.0 per cent, then inject a further 4 times and calculate, for the 6 injections, the relative standard deviation.

System suitability Reference solution (b):

— *repeatability*: maximum relative standard deviation of 2.0 per cent after 6 injections.

Calculate the content of isosorbide dinitrate as a percentage of the declared content.

STORAGE

Protected from light.

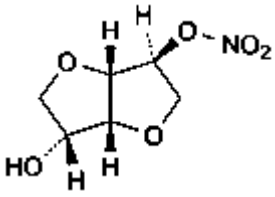
LABELLING

The label states the percentage content of isosorbide dinitrate.

IMPURITIES

Specified impurities *A, B, C.*

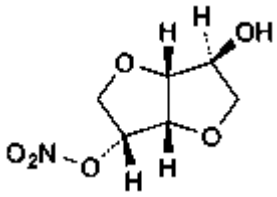
A. inorganic nitrates,



B. 1,4:3,6-dianhydro-D-glucitol 2-nitrate (isosorbide 2-nitrate),

www.webofpharma.com

https://thuocngocanh.com/



C. 1,4:3,6-dianhydro-D-glucitol 5-nitrate (isosorbide 5-nitrate, isosorbide mononitrate).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

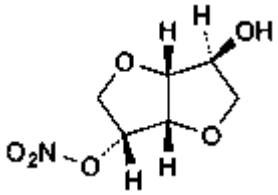
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diluted Isosorbide Mononitrate

General Notices

(Ph. Eur. monograph 1118)



$C_6H_9NO_6$ 191.1

Action and use

Nitric acid analogue; treatment of angina pectoris.

Preparations

Isosorbide Mononitrate Tablets

Isosorbide Mononitrate Prolonged-release Capsules

Isosorbide Mononitrate Prolonged-release Tablets

Ph Eur

DEFINITION

Dry mixture of isosorbide mononitrate and *Lactose monohydrate (0187)* or *Mannitol (0559)*.

Content

95.0 per cent *m/m* to 105.0 per cent *m/m* of the content of 1,4:3,6-dianhydro-D-glucitol 5-nitrate stated on the label.

CHARACTERS

Appearance

Undiluted isosorbide mononitrate is a white or almost white, crystalline powder.

Solubility

Undiluted isosorbide mononitrate is freely soluble in water, in acetone, in ethanol (96 per cent) and in methylene chloride.

www.webofpharma.com

https://thuocngocanh.com/

The solubility of the diluted product depends on the diluent and its concentration.

IDENTIFICATION

First identification: A, C, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs prepared with the residue obtained in identification test D.

Comparison *isosorbide mononitrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Shake a quantity of the substance to be examined corresponding to 10 mg of isosorbide mononitrate with 10 mL of *ethanol (96 per cent) R* for 5 min and filter.

Reference solution Dissolve 10 mg of *isosorbide mononitrate CRS* in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel G plate R*.

Mobile phase *methanol R*, *methylene chloride R* (5:95 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In a current of air.

Detection Spray with freshly prepared *potassium iodide and starch solution R*. Expose to ultraviolet light at 254 nm for 15 min and examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Thin-layer chromatography (2.2.27).

Test solution Shake a quantity of the substance to be examined corresponding to 0.10 g of lactose or mannitol with 10 mL of *water R*; filter if necessary.

Reference solution (a) Dissolve 0.10 g of *lactose monohydrate R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 0.10 g of *mannitol R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (c) Mix equal volumes of reference solutions (a) and (b).

Plate *TLC silica gel G plate R*.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase *water R*, *methanol R*, *anhydrous acetic acid R*, *ethylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately since a slight excess of water produces cloudiness.

Application 1 µL; thoroughly dry the points of application.

Development A Over a path of 15 cm.

Drying A In a current of warm air.

Development B Immediately, over a path of 15 cm, after renewing the mobile phase.

Drying B In a current of warm air.

Detection Spray with *4-aminobenzoic acid solution R* and dry in a current of cold air until the acetone is removed; heat at 100 °C for 15 min and allow to cool; spray with a 2 g/L solution of *sodium periodate R* and dry in a current of cold air; heat at 100 °C for 15 min.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a) for lactose or to the principal spot in the chromatogram obtained with reference solution (b) for mannitol.

D. Shake a quantity of the substance to be examined corresponding to 25 mg of isosorbide mononitrate with 10 mL of *acetone R* for 5 min. Filter, evaporate to dryness at a temperature below 40 °C and dry the residue over *diphosphorus pentoxide R* at a pressure of 0.7 kPa for 16 h. The melting point (*2.2.14*) of the residue is 89 °C to 91 °C.

TESTS

Impurity A

Thin-layer chromatography (*2.2.27*).

Test solution Shake a quantity of the substance to be examined corresponding to 0.10 g of isosorbide mononitrate with 5 mL of *ethanol (96 per cent) R* and filter.

Reference solution Dissolve 10 mg of *potassium nitrate R* in 1 mL of *water R* and dilute to 100 mL with *ethanol (96 per cent) R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *toluene R* (15:30:60 *V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In a current of air until the acetic acid is completely removed.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spray copiously with freshly prepared *potassium iodide and starch solution R*; expose to ultraviolet light at 254 nm for 15 min and examine in daylight.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the principal spot in the chromatogram obtained with the reference solution (0.5 per cent, calculated as potassium nitrate).

Impurities B and C

Liquid chromatography (*2.2.29*).

Test solution (a) Sonicate a quantity of the substance to be examined corresponding to 25.0 mg of isosorbide mononitrate with 20 mL of the mobile phase for 15 min and dilute to 25.0 mL with the mobile phase. Filter the solution through a suitable membrane filter.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *isosorbide mononitrate CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10.0 mg of *isosorbide-2-nitrate CRS* (impurity C) in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 0.1 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (c) Sonicate a quantity of *isosorbide dinitrate CRS* (impurity B) corresponding to 10.0 mg of isosorbide dinitrate in 15 mL of the mobile phase for 15 min and dilute to 20.0 mL with the mobile phase. Filter the solution through a suitable membrane filter. Dilute 0.1 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 5 mg of *isosorbide mononitrate CRS* and 5 mg of *isosorbide-2-nitrate CRS* (impurity C) in the mobile phase and dilute to 10 mL with the mobile phase. Dilute 1 mL of this solution to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (10 µm).

Mobile phase *anhydrous ethanol R*, *trimethylpentane R* (15:85 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 210-215 nm.

Injection 10 µL of test solution (a) and reference solutions (b), (c) and (d).

Retention time Impurity B = about 5 min; impurity C = about 8 min; isosorbide 5-nitrate = about 11 min.

System suitability Reference solution (d):

— *resolution*: minimum 4.0 between the peaks due to impurity C and isosorbide 5-nitrate.

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent).

ASSAY

Liquid chromatography (2.2.29) as described in the test for impurities B and C with the following modifications.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (b) and reference solution (a).

If the areas of the peaks from 2 successive injections of reference solution (a) do not agree to within 1.0 per cent, then inject a further 4 times and calculate, for the 6 injections, the relative standard deviation.

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 2.0 per cent after 6 injections.

Calculate the content of isosorbide mononitrate as a percentage of the declared content.

STORAGE

Protected from light.

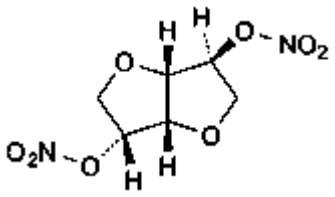
LABELLING

The label states the percentage content of isosorbide mononitrate.

IMPURITIES

Specified impurities *A, B, C.*

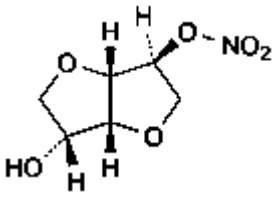
A. inorganic nitrates,



B. 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate (isosorbide dinitrate),

www.webofpharma.com

https://thuocngocanh.com/



C. 1,4:3,6-dianhydro-D-glucitol 2-nitrate (isosorbide 2-nitrate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

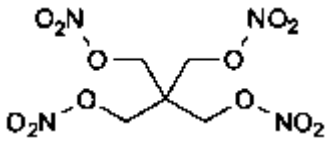
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diluted Pentaerythrityl Tetranitrate

General Notices

(Ph. Eur. monograph 1335)



$C_5H_8N_4O_{12}$ 316.1

Action and use

Vasodilator.

Ph Eur

DEFINITION

Dry mixture of 2,2-bis(hydroxymethyl)propane-1,3-diol tetranitrate (pentaerythrityl tetranitrate) and *Lactose monohydrate (0187)* or *Mannitol (0559)*.

Content

95.0 per cent *m/m* to 105.0 per cent *m/m* of the declared content of pentaerythrityl tetranitrate.

CAUTION: undiluted pentaerythrityl tetranitrate may explode if subjected to percussion or excessive heat. Appropriate precautions must be taken and only very small quantities handled.

CHARACTERS

Appearance of pentaerythrityl tetranitrate White or slightly yellowish powder.

Solubility of pentaerythrityl tetranitrate Practically insoluble in water, soluble in acetone, slightly soluble in ethanol (96 per cent).

The solubility of diluted pentaerythrityl tetranitrate depends on the diluent and its concentration.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Separately shake a quantity of the substance to be examined and a quantity of the reference substance, each corresponding to 25 mg of pentaerythrityl tetranitrate, with 10 mL of *acetone R* for 5 min; filter, evaporate to dryness at a temperature below 40 °C, and dry the residue over *diphosphorus pentoxide R* at a pressure of 0.7 kPa for 16 h. Examine the residues prepared as discs.

Comparison *diluted pentaerythrityl tetranitrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Shake a quantity of the substance to be examined corresponding to 10 mg of pentaerythrityl tetranitrate with 10 mL of *ethanol (96 per cent) R* for 5 min and filter.

Reference solution Shake a quantity of *diluted pentaerythrityl tetranitrate CRS* corresponding to 10 mg of pentaerythrityl tetranitrate with 10 mL of *ethanol (96 per cent) R* for 5 min and filter.

Plate *TLC silica gel plate R*.

Mobile phase *ethyl acetate R*, *toluene R* (20:80 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with freshly prepared *potassium iodide and starch solution R*, expose to ultraviolet light at 254 nm for 15 min and examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Thin-layer chromatography (2.2.27).

Test solution Shake a quantity of the substance to be examined corresponding to 0.10 g of lactose or mannitol with 10 mL of *water R*. Filter if necessary.

Reference solution (a) Dissolve 0.10 g of *lactose monohydrate R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 0.10 g of *mannitol R* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (c) Mix equal volumes of reference solutions (a) and (b).

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *methanol R*, *anhydrous acetic acid R*, *ethylene chloride R* (10:15:25:50 *V/V/V/V*). Measure the volumes accurately since a slight excess of water produces cloudiness.

Application 1 µL; thoroughly dry the points of application.

www.webofpharma.com

https://thuocngocanh.com/

Development A Over 2/3 of the plate.

Drying A In a current of warm air.

Development B Immediately, over 2/3 of the plate, after renewing the mobile phase.

Drying B In a current of warm air.

Detection Spray with *4-aminobenzoic acid solution R*, dry in a current of cold air until the acetone is removed, then heat at 100 °C for 15 min; allow to cool, spray with a 2 g/L solution of *sodium periodate R*, dry in a current of cold air and heat at 100 °C for 15 min.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a) for lactose or to the principal spot in the chromatogram obtained with reference solution (b) for mannitol.

TESTS

Impurity A

Thin-layer chromatography (*2.2.27*).

Test solution Shake a quantity of the substance to be examined corresponding to 0.10 g of pentaerythrityl tetranitrate with 5 mL of *ethanol (96 per cent) R* and filter.

Reference solution Dissolve 10 mg of *potassium nitrate R* in 1 mL of *water R* and dilute to 100 mL with *ethanol (96 per cent) R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *toluene R* (15:30:60 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of air until the acetic acid is completely removed.

Detection Spray copiously with freshly prepared *potassium iodide and starch solution R*, expose the plate to ultraviolet light at 254 nm for 15 min and examine in daylight.

Limit:

— *nitrate*: any spot due to nitrate is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent, calculated as potassium nitrate).

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29).

Test solution (a) Sonicate for 15 min a quantity of the substance to be examined corresponding to 25.0 mg of pentaerythrityl tetranitrate in 20 mL of the mobile phase and dilute to 25.0 mL with the mobile phase. Filter.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Sonicate for 15 min a quantity of *diluted pentaerythrityl tetranitrate CRS* corresponding to 25.0 mg of pentaerythrityl tetranitrate in 20 mL of the mobile phase and dilute to 25.0 mL with the mobile phase. Filter.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 0.3 mL of reference solution (b) to 10.0 mL with the mobile phase.

Reference solution (d) Dilute 200 µL of *glyceryl trinitrate solution CRS* to 25.0 mL with the mobile phase.

Reference solution (e) To 1 mL of reference solution (b) add 1 mL of reference solution (d) and dilute to 10 mL with the mobile phase.

Reference solution (f) Dilute 1.0 mL of reference solution (a) to 20.0 mL with the mobile phase. Dilute 0.5 mL of this solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water R*, *acetonitrile R* (35:65 *V/V*).

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (c), (e) and (f).

Run time 5 times the retention time of pentaerythrityl tetranitrate.

Relative retention With reference to pentaerythrityl tetranitrate (retention time = about 2.4 min): impurity B = about 0.7; impurity C = about 3.0.

System suitability Reference solution (e):

— *resolution*: minimum 3.0 between the peaks due to glyceryl trinitrate and pentaerythrityl tetranitrate.

Limits:

— *impurities C, D*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (f) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (f) (0.05 per cent).

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (b).

Calculate the percentage content of $C_5H_8N_4O_{12}$ from the declared content of *diluted pentaerythrityl tetranitrate CRS*.

STORAGE

Protected from light and heat.

LABELLING

The label states:

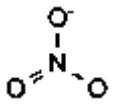
— the percentage content of pentaerythrityl tetranitrate;

— the diluent used.

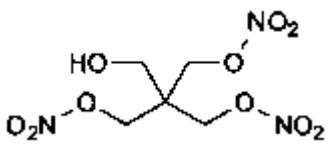
IMPURITIES

Specified impurities *A, C, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B.*



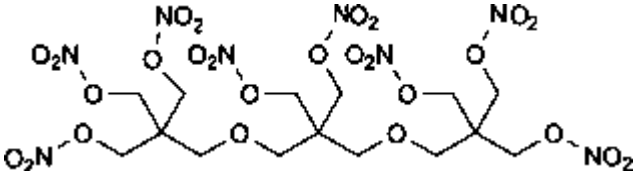
A. NO_3^-: inorganic nitrates,



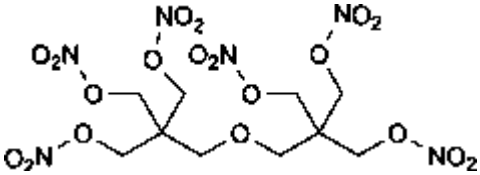
www.webofpharma.com

https://thuocngocanh.com/

B. 2,2-bis(hydroxymethyl)propane-1,3-diol trinitrate (pentaerythritol trinitrate),



C. 2,2-bis[[3-hydroxy-2,2-bis(hydroxymethyl)propoxy]methyl]propane-1,3-diol octanitrate (tripentaerythrityl octanitrate),



D. 2,2′-(oxybismethylene)bis[2-(hydroxymethyl)propane-1,3-diol] hexanitrate (dipentaerythrityl hexanitrate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

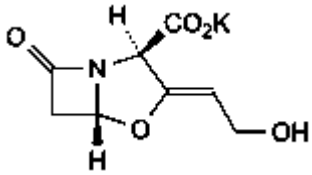
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diluted Potassium Clavulanate

General Notices

(Ph. Eur. monograph 1653)



$C_8H_8KNO_5$ 237.3

Action and use

Beta-lactamase inhibitor, potentiation of the action of amoxicillin and ticarcillin.

Preparations

Co-amoxiclav Oral Suspension

Co-amoxiclav Tablets

Co-amoxiclav Dispersible Tablets

Ph Eur

DEFINITION

Dry mixture of *Potassium clavulanate (1140)* and *Cellulose, microcrystalline (0316)* or *Silica, colloidal anhydrous (0434)* or *Silica, colloidal hydrated (0738)*.

Content

91.2 per cent to 107.1 per cent of the content of potassium clavulanate stated on the label.

CHARACTERS

Appearance of diluted potassium clavulanate White or almost white powder, hygroscopic.

Solubility of potassium clavulanate Freely soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in acetone.

The solubility of the diluted product depends on the diluent and its concentration.

IDENTIFICATION

https://thuocngocanh.com/

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. It gives reaction (b) of potassium (2.3.1).

C. Depending on the diluent used, carry out the corresponding identification test (a) or (b).

(a) A quantity of the substance to be examined, corresponding to 20 mg of cellulose, when placed on a watch-glass and dispersed in 4 mL of *iodinated zinc chloride solution R*, becomes violet-blue.

(b) It gives the reaction of silicates (2.3.1).

TESTS

pH (2.2.3)

4.8 to 8.0.

Suspend a quantity of the substance to be examined corresponding to 0.200 g of potassium clavulanate in 20 mL of *carbon dioxide-free water R*.

Polymeric impurities and other impurities absorbing at 278 nm

Disperse a quantity of the substance to be examined corresponding to 50.0 mg of potassium clavulanate in 10 mL of *0.1 M phosphate buffer solution pH 7.0 R*, dilute to 50.0 mL with the same buffer solution and filter. Measure the absorbance immediately.

The absorbance (2.2.25) of the solution determined at 278 nm is not greater than 0.40.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Disperse a quantity of the substance to be examined corresponding to 0.250 g of potassium clavulanate in 5 mL of mobile phase A, dilute to 25.0 mL with mobile phase A and filter.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (b) Dissolve 10 mg of *amoxicillin trihydrate CRS* in 1 mL of the test solution and dilute to 100 mL with mobile phase A.

Reference solution (c) 2 mg of *potassium clavulanate impurity G CRS* in 20 mL of mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: 7.8 g/L solution of *sodium dihydrogen phosphate R* adjusted to pH 4.0 with *dilute phosphoric acid R*;

— *mobile phase B*: a mixture of equal volumes of mobile phase A and *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	100	0
4 - 15	100 → 50	0 → 50
15 - 18	50	50

Flow rate 1 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity G.

Relative retention With reference to clavulanate (retention time = about 3 min): impurity E = about 2.3; impurity G = about 3.6.

System suitability Reference solution (b):

— *resolution*: minimum 13 between the peaks due to clavulanate (1st peak) and amoxicillin (2nd peak).

Limits:

— *impurities E, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 1.000 g.

ASSAY

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

www.webofpharma.com

https://thuocngocanh.com/

Test solution Disperse a quantity of the substance to be examined corresponding to 50.0 mg of potassium clavulanate in a 4.1 g/L solution of *sodium acetate R* previously adjusted to pH 6.0 with *glacial acetic acid R*, dilute to 50.0 mL with the same solution and filter.

Reference solution (a) Dissolve 50.0 mg of *lithium clavulanate CRS* in a 4.1 g/L solution of *sodium acetate R* previously adjusted to pH 6.0 with *glacial acetic acid R* and dilute to 50.0 mL with the same solution.

Reference solution (b) Dissolve 10 mg of *amoxicillin trihydrate CRS* in 10 mL of reference solution (a).

Column:

— *size*: *l* = 0.3 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase Mix 5 volumes of *methanol R1* and 95 volumes of a 15 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 4.0 with *dilute phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

System suitability Reference solution (b):

— *resolution*: minimum 3.5 between the peaks due to clavulanate (1st peak) and amoxicillin (2nd peak).

1 mg of $C_8H_9NO_5$ is equivalent to 1.191 mg of $C_8H_8KNO_5$.

STORAGE

In an airtight container.

LABELLING

The label states the percentage content of potassium clavulanate and the diluent used to prepare the mixture.

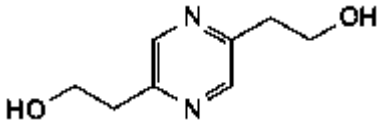
IMPURITIES

Specified impurities *E, G.*

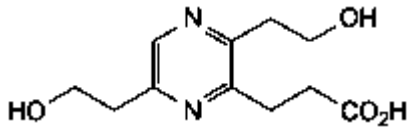
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, F.*

www.webofpharma.com

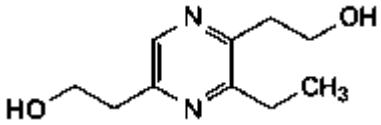
https://thuocngocanh.com/



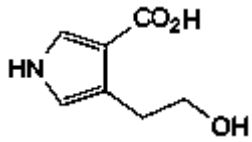
A. 2,2′-(pyrazine-2,5-diyl)diethanol,



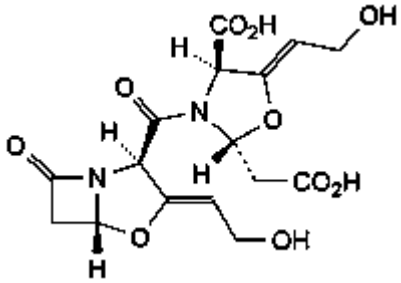
B. 3-[3,6-bis(2-hydroxyethyl)pyrazin-2-yl]propanoic acid,



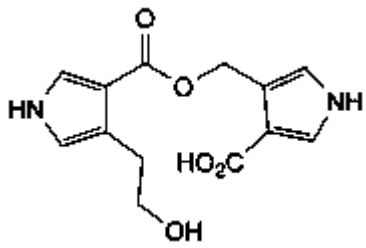
C. 2,2′-(3-ethylpyrazine-2,5-diyl)diethanol,



D. 4-(2-hydroxyethyl)-1*H*-pyrrole-3-carboxylic acid,



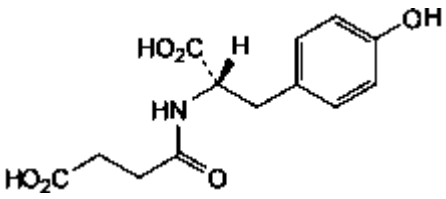
E. (2*R*,4*R*,5*Z*)-2-(carboxymethyl)-5-(2-hydroxyethylidene)-3-[[(2*R*,3*Z*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]oxazolidine-4-carboxylic acid,



F. 4-[[[[4-(2-hydroxyethyl)-1*H*-pyrrol-3-yl]carbonyl]oxy]methyl]-1*H*-pyrrole-3-carboxylic acid,

www.webofpharma.com

https://thuocngocanh.com/



G. 4-[[(1*S*)-1-carboxy-2-(4-hydroxyphenyl)ethyl]amino]-4-oxobutanoic acid (*N*-(hydrogensuccinyl)tyrosine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

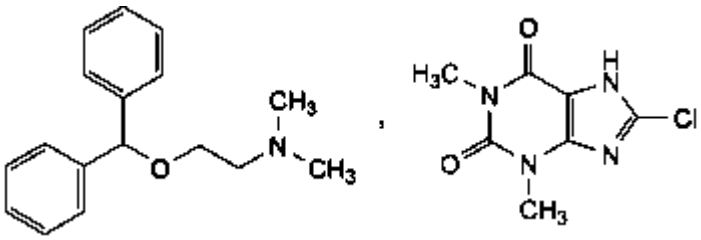
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimenhydrinate

General Notices

(Ph. Eur. monograph 0601)



$C_{24}H_{28}ClN_5O_3$ 470.0 *523-87-5*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Preparation

Dimenhydrinate Tablets

Ph Eur

DEFINITION

Diphenhydramine [2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine] 8-chlorotheophylline (8-chloro-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione).

Content

— *diphenhydramine* ($C_{17}H_{21}NO$; M_r 255.4): 53.0 per cent to 55.5 per cent (dried substance);

— *8-chlorotheophylline* ($C_7H_7ClN_4O_2$; M_r 214.6): 44.0 per cent to 46.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Slightly soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 102 °C to 106 °C.

B. Dissolve 0.1 g in a mixture of 3 mL of water R and 3 mL of ethanol (96 per cent) R, add 6 mL of water R and 1 mL of dilute hydrochloric acid R and cool in iced water for 30 min, scratching the wall of the tube with a glass rod if necessary to initiate crystallisation. Dissolve about 10 mg of the precipitate obtained in 1 mL of hydrochloric acid R, add 0.1 g of potassium chlorate R and evaporate to dryness in a porcelain dish. A reddish residue is obtained that becomes violet-red when exposed to ammonia vapour.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison dimenhydrinate CRS.

D. Dissolve 0.2 g in 10 mL of ethanol (96 per cent) R. Add 10 mL of picric acid solution R and initiate crystallisation by scratching the wall of the tube with a glass rod. The precipitate, washed with water R and dried at 100-105 °C, melts (2.2.14) at 130 °C to 134 °C.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 1.0 g in ethanol (96 per cent) R and dilute to 20 mL with the same solvent.

pH (2.2.3)

7.1 to 7.6 for the filtrate.

To 0.4 g add 20 mL of carbon dioxide-free water R, shake for 2 min and filter.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (18:82 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 57 mg of diphenhydramine hydrochloride CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Dissolve 5.0 mg of *diphenhydramine impurity A CRS* (impurity F) in 5.0 mL of reference solution (a) and dilute to 50.0 mL with the solvent mixture.

Reference solution (d) Dissolve the contents of a vial of *dimenhydrinate for peak identification CRS* (containing impurities A and E) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: dissolve 10.0 g of *triethylamine R2* in 950 mL of *water R*, adjust to pH 2.5 with *phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 2	82	18	1.2
2 - 15	82 → 50	18 → 50	1.2
15 - 20	50 → 20	50 → 80	1.2 → 2.0
20 - 30	20	80	2.0

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *dimenhydrinate for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A and E; use the chromatogram obtained with reference solution (c) to identify impurity F.

Relative retention With reference to diphenhydramine (retention time = about 13 min): impurity A = about 0.3; impurity E = about 0.7; impurity F = about 0.95.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity F and diphenhydramine.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurities A, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity E*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo*.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Diphenhydramine

Dissolve 0.200 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.54 mg of $C_{17}H_{21}NO$.

8-Chlorotheophylline

To 0.800 g add 50 mL of *water R*, 3 mL of *dilute ammonia R1* and 0.6 g of *ammonium nitrate R* and heat on a water-bath for 5 min. Add 25.0 mL of *0.1 M silver nitrate* and continue heating on a water-bath for 15 min with frequent swirling. Cool, add 25 mL of *dilute nitric acid R* and dilute to 250.0 mL with *water R*. Filter and discard the first 25 mL of the filtrate. Using 5 mL of *ferric ammonium sulfate solution R2* as indicator, titrate 100.0 mL of the filtrate with *0.1 M ammonium thiocyanate* until a yellowish-brown colour is obtained.

1 mL of *0.1 M silver nitrate* is equivalent to 21.46 mg of $C_7H_7ClN_4O_2$.

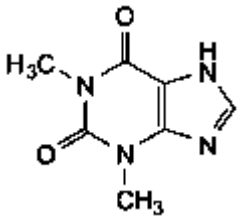
IMPURITIES

Specified impurities *A, E, F.*

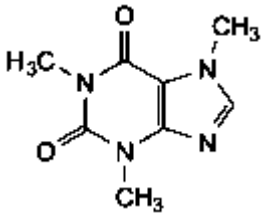
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, G, H, I, J, K.*

www.webofpharma.com

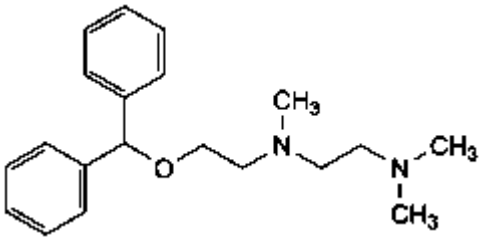
https://thuocngocanh.com/



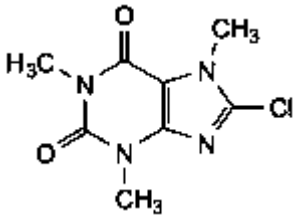
A. 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theophylline),



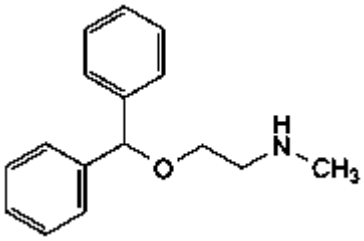
C. 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (caffeine),



D. *N*-[2-(diphenylmethoxy)ethyl]-*N*,*N*′,*N*′-trimethylethane-1,2-diamine,



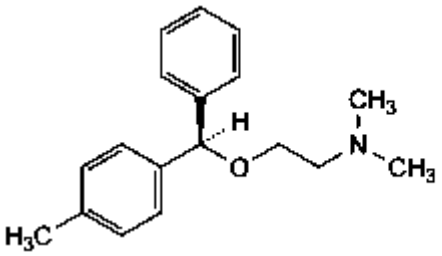
E. 8-chloro-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (8-chlorocaffeine),



F. 2-(diphenylmethoxy)-*N*-methylethanamine (diphenhydramine impurity A),

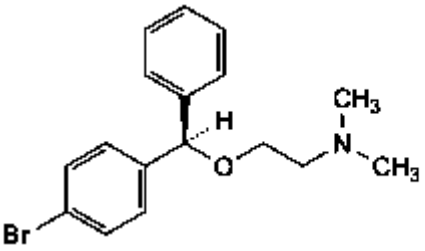
www.webofpharma.com

https://thuocngocanh.com/



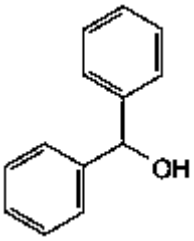
and enantiomer

G. *N*,*N*-dimethyl-2-[(*RS*)-(4-methylphenyl)(phenyl)methoxy]ethanamine (4-methyldiphenhydramine),

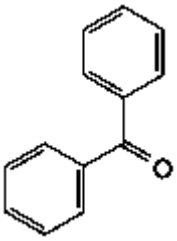


and enantiomer

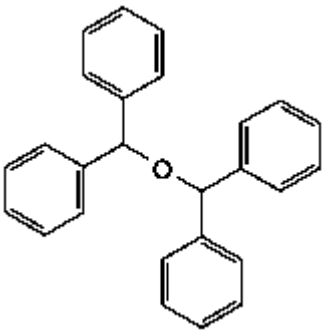
H. 2-[(*RS*)-(4-bromophenyl)-(phenyl)methoxy]-*N*,*N*-dimethylethanamine (4-bromodiphenhydramine),



I. diphenylmethanol (benzhydrol),



J. diphenylmethanone (benzophenone),



K. [oxybis(methanetriyl)]tetrabenzene.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimenhydrinate Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Dimenhydrinate Tablets contain Dimenhydrinate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dimenhydrinate, $C_{17}H_{21}NO,C_7H_7ClN_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.1 g of Dimenhydrinate with 10 mL of a mixture of equal volumes of *chloroform* and *ether* for 5 minutes, filter and evaporate the filtrate to an oily residue on a water bath. Add 3 mL of *ether* to the residue and scratch the interface between the residue and the ether gently with a glass rod until crystals appear in the liquid. Transfer the suspension of crystalline material in ether to a watch glass, allow the solvent to evaporate in a current of air and dry the residue at 60°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dimenhydrinate *(RS 104)*.

TESTS

Theophylline and substances related to diphenhydramine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Dimenhydrinate with three 10-mL quantities of *chloroform*, filter, evaporate the combined filtrates almost to dryness and dissolve the residue in 5 mL of *chloroform*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *chloroform*.

(3) 0.010% w/v of *theophylline* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

www.webofpharma.com

https://thuvienthuocngocanh.com/

(e) After removal of the plate, dry in a current of cold air and examine under *ultraviolet light (254 nm)* (first examination). Spray the plate with *potassium iodobismuthate solution*, allow it to dry in air and spray with *hydrogen peroxide solution (10 vol)* and examine in daylight (second examination).

MOBILE PHASE

1 volume of 13.5M *ammonia*, 9 volumes of *methanol* and 90 volumes of *dichloromethane*.

LIMITS

In the first examination:

any spot corresponding to theophylline in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%).

In the second examination:

any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

Disregard any spot extending from the line of application to an Rf value of about 0.1.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.1 g of Dimenhydrinate as completely as possible in 20 mL of *water*, add 10 mL of 5M *ammonia*, mix, extract with successive quantities of 15, 15, 15, 10 and 10 mL of *ether* and wash the combined extracts with 10 mL of *water*. Evaporate the ether, warm the residue with 10 mL of *ethanol (96%)* until dissolved, cool, add 50 mL of *0.01M hydrochloric acid VS* and titrate the excess of acid with *0.01M sodium hydroxide VS* using *methyl red mixed solution* as indicator. Each mL of *0.01M hydrochloric acid VS* is equivalent to 4.700 mg of $C_{17}H_{21}NO,C_7H_7ClN_4O_2$.

© Crown Copyright 2022

www.webofpharma.com

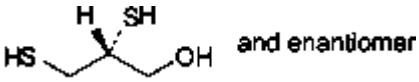
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimercaprol

General Notices

(Ph. Eur. monograph 0389)



$C_3H_8OS_2$ 124.2 *59-52-9*

Action and use

Chelating agent for use in heavy metal poisoning.

Preparation

Dimercaprol Injection

When B.A.L. is prescribed or demanded, Dimercaprol shall be dispensed or supplied.

Ph Eur

DEFINITION

(2*RS*)-2,3-Disulfanylpropan-1-ol.

Content

98.5 per cent to 101.5 per cent.

CHARACTERS

Appearance

Clear, colourless or slightly yellow liquid.

Solubility

Soluble in water and in arachis oil, miscible with ethanol (96 per cent) and with benzyl benzoate.

IDENTIFICATION

A. Dissolve 0.05 mL in 2 mL of *water R*. Add 1 mL of *0.05 M iodine*. The colour of the iodine is discharged immediately.

www.webofpharma.com

https://thuocngocanh.com/

B. Dissolve 0.1 mL in 5 mL of *water R* and add 2 mL of *copper sulfate solution R*. A bluish-black precipitate is formed which quickly becomes dark grey.

C. In a ground-glass-stoppered tube, suspend 0.6 g of *sodium bismuthate R*, previously heated to 200 °C for 2 h, in a mixture of 2.8 mL of *dilute phosphoric acid R* and 6 mL of *water R*. Add 0.2 mL of the substance to be examined, mix and allow to stand for 10 min with frequent shaking. To 1 mL of the supernatant add 5 mL of a 4 g/L solution of *chromotropic acid, sodium salt R* in *sulfuric acid R* and mix. Heat in a water-bath for 15 min. A violet-red colour develops.

TESTS

Appearance

It is clear (*2.2.1*) and not more intensely coloured than reference solution B_6 or BY_6 (*2.2.2, Method II*).

Acidity or alkalinity

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Add 0.25 mL of *bromocresol green solution R* and 0.3 mL of *0.01 M hydrochloric acid*. The solution is yellow. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Refractive index (*2.2.6*)

1.568 to 1.574.

Halides

To 2.0 g add 25 mL of *alcoholic potassium hydroxide solution R* and boil under a reflux condenser for 2 h. Eliminate the ethanol by evaporation in a stream of hot air. Add 20 mL of *water R* and cool. Add 40 mL of *water R* and 10 mL of *strong hydrogen peroxide solution R*, boil gently for 10 min, cool and filter rapidly. Add 10 mL of *dilute nitric acid R* and 5.0 mL of *0.1 M silver nitrate*. Using 2 mL of *ferric ammonium sulfate solution R2* as indicator, titrate with *0.1 M ammonium thiocyanate* until a reddish-yellow colour is obtained. Carry out a blank titration. The difference between the titration volumes is not greater than 1.0 mL.

ASSAY

Dissolve 0.100 g in 40 mL of *methanol R*. Add 20 mL of *0.1 M hydrochloric acid* and 50.0 mL of *0.05 M iodine*. Allow to stand for 10 min and titrate with *0.1 M sodium thiosulfate*. Carry out a blank titration.

1 mL of *0.05 M iodine* is equivalent to 6.21 mg of $C_3H_8OS_2$.

STORAGE

In a well-filled, airtight container, protected from light, at a temperature of 2 °C to 8 °C.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimercaprol Injection

General Notices

Action and use

Chelating agent for use in heavy metal poisoning.

DEFINITION

Dimercaprol Injection contains 5% w/v of Dimercaprol in a suitable vehicle.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of dimercaprol, $C_3H_8OS_2$

4.75 to 5.25% w/v.

CHARACTERISTICS

A bright, pale yellow solution.

TESTS

Acidity

Shake with an equal volume of *water* for 2 minutes and allow to separate. The pH of the aqueous layer, after filtration through neutral filter paper, is 4.5 to 6.5, Appendix V L.

Refractive index

1.482 to 1.486, Appendix V E.

Weight per mL

0.940 to 0.955 g, Appendix V G.

ASSAY

To 1 g add 20 mL of *0.1M hydrochloric acid* and titrate with *0.05M iodine VS*. Each mL of *0.05M iodine VS* is equivalent to 6.21 mg of $C_3H_8OS_2$. Use the *weight per mL* of the injection to calculate the percentage w/v of $C_3H_8OS_2$.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Dimercaprol Injection should be protected from light.

LABELLING

The label states (1) the nature of the solvent; (2) that the preparation is intended for intramuscular injection only.

© Crown Copyright 2022

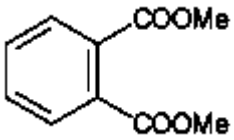
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimethyl Phthalate

General Notices



$C_{10}H_{10}O_4$ 194.2 *131-11-3*

Action and use

Insect repellent.

DEFINITION

Dimethyl Phthalate contains not less than 99.0% and not more than 100.5% w/w of $C_{10}H_{10}O_4$.

CHARACTERISTICS

A colourless or faintly coloured liquid.

Slightly soluble in *water*; miscible with *ethanol (96%)*, with *ether* and with most organic solvents.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of dimethyl phthalate *(RS 105)*.

B. Gently boil 1 g with 5 mL of 2M *methanolic potassium hydroxide* for 10 minutes, add 5 mL of *water*, evaporate the mixture to half its volume and cool. Add 1 mL of *hydrochloric acid*, filter, melt the dried precipitate in a small tube, add 0.5 g of *resorcinol* and 0.05 mL of *chloroform* and heat to about 180° for 3 minutes. Cool, add 1 mL of 5M *sodium hydroxide* and pour into *water*. An intense yellowish green fluorescence is produced.

TESTS

Acidity

Mix 20 mL with 50 mL of *ethanol (96%)* previously neutralised to *phenolphthalein solution R1*. Not more than 0.1 mL of *0.1M sodium hydroxide VS* is required to neutralise the solution using *phenolphthalein solution R1* as indicator.

Refractive index

www.webofpharma.com

https://thuocngocanh.com/

1.515 to 1.517, Appendix V E.

Weight per mL

1.186 to 1.192 g, Appendix V G.

Related substances

Prepare a 0.075% w/v solution of *phenyl benzoate* (internal standard) in *chloroform* (solution A). Carry out the method for *gas chromatography*, Appendix III B, using solutions of the substance being examined containing (1) 0.10% w/v in solution A, (2) 5.0% w/v in *chloroform* and (3) 5.0% w/v in solution A.

The chromatographic procedure may be carried out using a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (80 to 100 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable) and maintained at 145°.

In the chromatogram obtained with solution (3) the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than the ratio of the area of the peak due to dimethyl phthalate to the area of the peak due to the internal standard in the chromatogram obtained with solution (1).

Sulfated ash

Not more than 0.1% w/w, Appendix IX A.

Water

Not more than 0.1% w/w, Appendix IX C. Use 20 g.

ASSAY

In a borosilicate glass flask dissolve 1.5 g of the substance being examined in 5 mL of carbon dioxide-free ethanol prepared by boiling *ethanol (96%)* thoroughly and neutralising to *phenolphthalein solution R1*. Neutralise the free acid in the solution with *0.1M ethanolic potassium hydroxide VS* using 0.2 mL of *phenolphthalein solution R1* as indicator. Add 50 mL of *0.5M ethanolic potassium hydroxide VS* and boil under a reflux condenser on a water bath for 1 hour. Add 20 mL of *water* and titrate the excess of alkali with *0.5M hydrochloric acid VS* using a further 0.2 mL of *phenolphthalein solution R1* as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the alkali required to saponify the esters. Each mL of *0.5M ethanolic potassium hydroxide VS* is equivalent to 48.55 mg of $C_{10}H_{10}O_4$.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

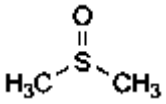
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimethyl Sulfoxide

General Notices

(Ph. Eur. monograph 0763)



C_2H_6OS 78.1 *67-68-5*

Action and use

Pharmaceutical solvent; excipient.

When dimethyl sulphoxide is demanded, Dimethyl Sulfoxide shall be supplied.

Ph Eur

DEFINITION

(Methanesulfinyl)methane.

CHARACTERS

Appearance

Colourless liquid or colourless crystals, hygroscopic.

Solubility

Miscible with water and with ethanol (96 per cent).

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Relative density (see Tests).

B. Refractive index (see Tests).

C. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *dimethyl sulfoxide CRS*.

D. Dissolve 50 mg of *nickel chloride R* in 5 mL of the substance to be examined. The solution is greenish-yellow. Heat in a water-bath at 50 °C. The colour changes to green or bluish-green. Cool. The colour changes to greenish-yellow.

TESTS

Acidity

Dissolve 50.0 g in 100 mL of *carbon dioxide-free water R*. Add 0.1 mL of *phenolphthalein solution R1*. Not more than 5.0 mL of *0.01 M sodium hydroxide* is required to produce a pink colour.

Relative density (*2.2.5*)

1.100 to 1.104.

Refractive index (*2.2.6*)

1.478 to 1.480.

Freezing point (*2.2.18*)

Minimum 18.3 °C.

Absorbance (*2.2.25*)

Purge with *nitrogen R* for 15 min. The absorbance, measured using *water R* as the compensation liquid, is not more than 0.30 at 275 nm and not more than 0.20 at both 285 nm and 295 nm. The substance to be examined shows no absorption maximum between 270 nm and 350 nm.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution The substance to be examined.

Reference solution (a) Dissolve 50 mg of the substance to be examined and 50 mg of *dimethyl sulfone R* (impurity A) in *methylene chloride R* and dilute to 100 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with *methylene chloride R*. Dilute 0.5 mL of this solution to 100.0 mL with *methylene chloride R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Carrier gas helium for chromatography R.

Flow rate 1.5 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	70
	6 - 24	70 → 250
Injection port		280
Detector		280

Detection Flame ionisation.

Injection 0.4 µL.

Relative retention With reference to dimethyl sulfoxide (retention time = about 5.4 min): impurity A = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to dimethyl sulfoxide and impurity A.

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.15 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)).

Water (*2.5.32*)

Maximum 0.2 per cent, determined on 1.00 g.

STORAGE

In an airtight, glass container, protected from light.

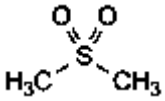
IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

www.webofpharma.com

https://thuocngocanh.com/

Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



A. (methanesulfonyl)methane (dimethyl sulfone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

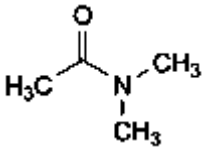
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimethylacetamide

General Notices

(Ph. Eur. monograph 1667)



C_4H_9NO 87.1 *127-19-5*

Action and use

Excipient.

Ph Eur

DEFINITION

N,*N*-Dimethylacetamide.

CHARACTERS

Appearance

Clear, colourless, slightly hygroscopic liquid.

Solubility

Miscible with water, with ethanol (96 per cent), and with most common organic solvents.

bp

About 165 °C.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Relative density (2.2.5): 0.941 to 0.944.

B. Refractive index (2.2.6): 1.435 to 1.439.

C. Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Preparation Films.

Comparison *Ph. Eur. reference spectrum of dimethylacetamide*.

D. Dilute 50 mg with 1 mL of *methanol R*. Add 1 mL of a 15 g/L solution of *hydroxylamine hydrochloride R* and mix. Add 1 mL of *dilute sodium hydroxide solution R*, mix and allow to stand for 30 min. Add 1 mL of *dilute hydrochloric acid R* and add 1 mL of a 100 g/L solution of *ferric chloride R* in *0.1 M hydrochloric acid*. A reddish-brown colour develops, reaching a maximum intensity after about 5 min.

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Acidity

Dilute 50 mL with 50 mL of *water R* previously adjusted with *0.02 M potassium hydroxide* or *0.02 M hydrochloric acid* to a bluish-green colour, using 0.5 mL of *bromothymol blue solution R1* as indicator. Not more than 5.0 mL of *0.02 M potassium hydroxide* is required to restore the initial (bluish-green) colour.

Alkalinity

To 50 mL add 50 mL of *water R* previously adjusted with *0.02 M potassium hydroxide* or *0.02 M hydrochloric acid* to a yellow colour, using 0.5 mL of *bromothymol blue solution R1* as indicator. Not more than 0.5 mL of *0.02 M hydrochloric acid* is required to restore the initial (yellow) colour.

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution The substance to be examined.

Reference solution (a) Dilute a mixture of 1 mL of the substance to be examined and 1 mL of *dimethylformamide R* (impurity B) to 20 mL with *methylene chloride R*.

Reference solution (b) Dilute 1 mL of the substance to be examined to 20.0 mL with *methylene chloride R*. Dilute 0.1 mL of the solution to 10.0 mL with *methylene chloride R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *macrogol 20 000 R* (film thickness 1 µm).

Carrier gas *nitrogen for chromatography R*.

www.webofpharma.com

https://thuocngocanh.com/

Linear velocity 30 cm/s.

Split ratio 1:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 15	80 → 200
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 0.5 µL.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to dimethylacetamide and impurity B in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

— *any impurity*: maximum 0.1 per cent;

— *total*: maximum 0.3 per cent;

— *disregard limit*: the area of the peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Non-volatile matter

Maximum 20 ppm.

Evaporate 50 g to dryness by suitable means at a pressure not exceeding 1 kPa and on a water-bath. Dry the residue in an oven at 170-175 °C. The residue weighs not more than 1 mg.

Water (*2.5.32*)

Maximum 0.1 per cent, determined on 0.100 g.

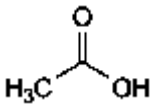
STORAGE

In an airtight container, protected from light.

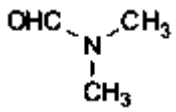
www.webofpharma.com

https://thuocngocanh.com/

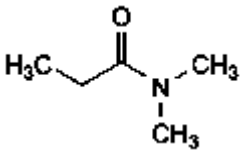
IMPURITIES



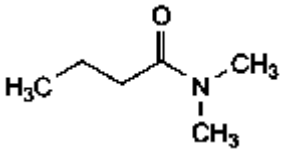
A. acetic acid,



B. *N*,*N*-dimethylformamide,



C. *N*,*N*-dimethylpropanamide,



D. *N*,*N*-dimethylbutanamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

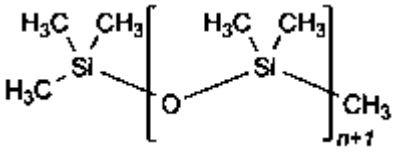
https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimeticone

General Notices

(Ph. Eur. monograph 0138)



9006-65-9

Action and use

Antifoaming agent; water repellent.

When dimethicone is demanded, Dimeticone shall be supplied.

Ph Eur

DEFINITION

α-Trimethylsilyl-ω-methylpoly[oxy(dimethylsilanediyl)].

This poly(dimethylsiloxane) is obtained by hydrolysis and polycondensation of dichlorodimethylsilane and chlorotrimethylsilane. Different grades of dimeticone exist which are distinguished by a number indicating the nominal kinematic viscosity placed after the name.

Their degree of polymerisation (*n* = 20 to 400) is such that their kinematic viscosities are nominally between 20 $mm^2 \cdot s^{-1}$ and 1300 $mm^2 \cdot s^{-1}$.

Dimeticones with a nominal viscosity of 50 $mm^2 \cdot s^{-1}$ or lower are intended for external use only.

CHARACTERS

Appearance

Clear, colourless liquid of various viscosities.

Solubility

Practically insoluble in water, very slightly soluble or practically insoluble in anhydrous ethanol, miscible with ethyl acetate, with methyl ethyl ketone and with toluene.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. It is identified by its kinematic viscosity at 25 °C (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dimeticone CRS*.

The region of the spectrum from 850 cm^{-1} to 750 cm^{-1} is not taken into account.

C. Heat 0.5 g in a test-tube over a small flame until white fumes begin to appear. Invert the tube over a 2nd tube containing 1 mL of a 1 g/L solution of *chromotropic acid, sodium salt R* in *sulfuric acid R* so that the fumes reach the solution. Shake the 2nd tube for about 10 s and heat on a water-bath for 5 min. The solution is violet.

D. In a platinum crucible, prepare the sulfated ash (2.4.14) using 50 mg. The residue is a white powder that gives the reaction of silicates (2.3.1).

TESTS

Acidity

To 2.0 g add 25 mL of a mixture of equal volumes of *anhydrous ethanol R* and *ether R*, previously neutralised to 0.2 mL of *bromothymol blue solution R1*, and shake. Not more than 0.15 mL of *0.01 M sodium hydroxide* is required to change the colour of the solution to blue.

Viscosity (2.2.9)

90 per cent to 110 per cent of the nominal kinematic viscosity stated on the label, determined at 25 °C.

Mineral oils

Place 2 g in a test-tube and examine in ultraviolet light at 365 nm. The fluorescence is not more intense than that of a solution containing 0.1 ppm of *quinine sulfate R* in *0.005 M sulfuric acid* examined in the same conditions.

Phenylated compounds

Dissolve 5.0 g with shaking in 10 mL of *cyclohexane R*. At wavelengths from 250 nm to 270 nm, the absorbance (2.2.25) of the solution is not greater than 0.2.

Volatile matter

Maximum 0.3 per cent, for dimeticones with a nominal viscosity greater than 50 $mm^2 \cdot s^{-1}$, determined on 1.00 g by heating in an oven at 150 °C for 2 h. Carry out the test using a dish 60 mm in diameter and 10 mm deep.

LABELLING

The label states:

— the nominal kinematic viscosity by a number placed after the name of the product;

www.webofpharma.com

https://thuocngocanh.com/

— where applicable, that the product is intended for external use.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for dimeticone used as emollient.

Viscosity

(see Tests).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

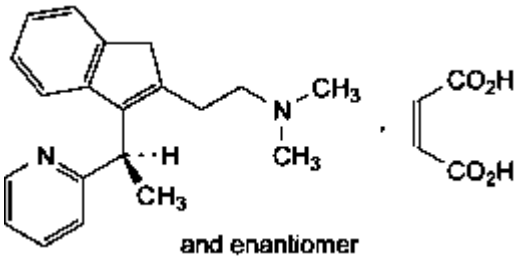
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dimetindene Maleate

General Notices

(Ph. Eur. monograph 1417)



$C_{24}H_{28}N_2O_4$ 408.5 *3614-69-5*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

N,*N*-Dimethyl-2-[3-[(1*RS*)-1-(pyridin-2-yl)ethyl]-1*H*-inden-2-yl]ethan-1-amine (2*Z*)-but-2-enedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, soluble in methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *dimetindene maleate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 0.20 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than Y_6 (*2.2.2, Method II*).

Optical rotation (*2.2.7*)

-0.10° to + 0.10°, determined on solution S.

Related substances

Gas chromatography (*2.2.28*).

Solvent mixture *acetone R*, *methylene chloride R* (50:50 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *2-ethylpyridine R* (impurity A) in the solvent mixture and dilute to 100 mL with the solvent mixture (solution A). Dissolve 50 mg of the substance to be examined in the solvent mixture, add 1 mL of solution A and dilute to 5 mL with the solvent mixture.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.45 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 1	60
	1 - 34.3	60 → 260

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
	34.3 - 46.3	260
Injection port		240
Detector		260

Detection Flame ionisation.

Injection 2 µL; inject via a split injector with a split flow of 30 mL/min.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurity A and maleic acid.

Relative retention With reference to dimetindene (retention time = about 36 min): impurity A = about 0.14; maleic acid = about 0.18.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity A and maleic acid in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 1.3 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— for each impurity, use the concentration of dimetindene maleate in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to maleic acid.

Loss on drying (2.2.32)

Maximum 0.1 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 80 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

www.webofpharma.com

https://thuocngocanh.com/

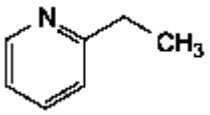
1 mL of *0.1 M perchloric acid* is equivalent to 20.43 mg of $C_{24}H_{28}N_2O_4$.

STORAGE

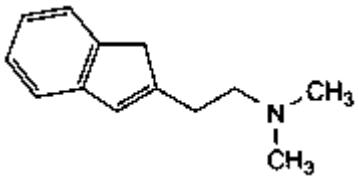
Protected from light.

IMPURITIES

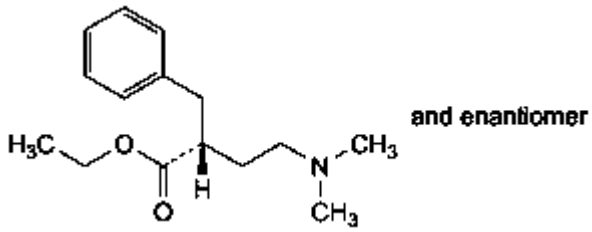
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H, I.



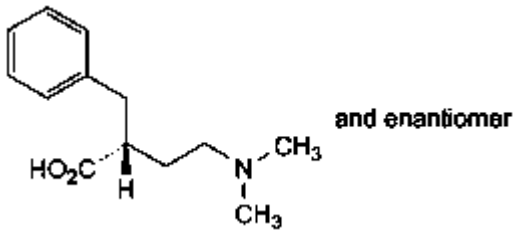
A. 2-ethylpyridine,



B. 2-(1*H*-inden-2-yl)-*N*,*N*-dimethylethan-1-amine,



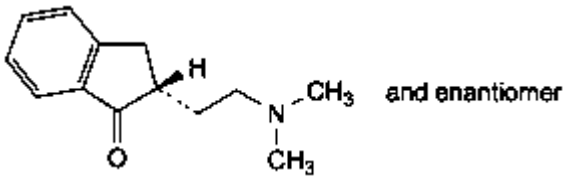
C. ethyl (2*RS*)-2-benzyl-4-(dimethylamino)butanoate,



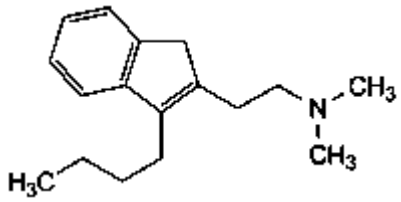
D. (2*RS*)-2-benzyl-4-(dimethylamino)butanoic acid,

www.webofpharma.com

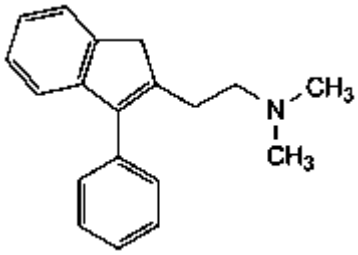
https://thuocngocanh.com/



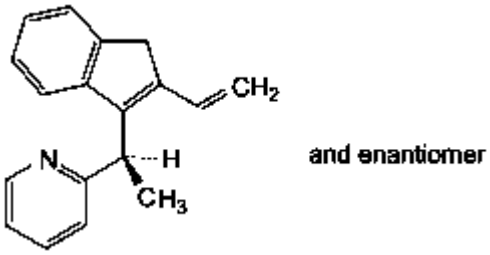
E. (2*RS*)-2-[2-(dimethylamino)ethyl]-2,3-dihydro-1*H*-inden-1-one,



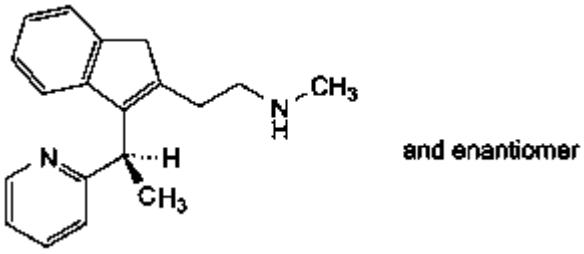
F. 2-(3-butyl-1*H*-inden-2-yl)-*N*,*N*-dimethylethan-1-amine,



G. *N*,*N*-dimethyl-2-(3-phenyl-1*H*-inden-2-yl)ethan-1-amine,



H. 2-[(1*RS*)-1-(2-ethenyl-1*H*-inden-3-yl)ethyl]pyridine,



I. *N*-methyl-2-[3-[(1*RS*)-1-(pyridin-2-yl)ethyl]-1*H*-inden-2-yl]ethan-1-amine.

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

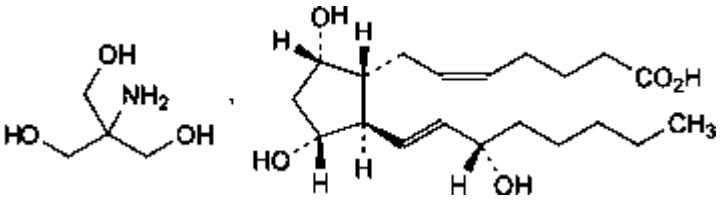
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dinoprost Trometamol

General Notices

(Ph. Eur. monograph 1312)



$C_{24}H_{45}NO_8$ 475.6 *38562-01-5*

Action and use

Prostaglandin $F_{2\alpha}$($PGF_{2\alpha}$); inducer of uterine muscle contraction.

Ph Eur

DEFINITION

Trometamol (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoate ($PGF_{2\alpha}$).

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), practically insoluble in acetonitrile.

IDENTIFICATION

A. Specific optical rotation (2.2.7): + 19 to + 26 (anhydrous substance).

Dissolve 0.100 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *dinoprost trometamol CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (23:77 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a). Degradation of dinoprost trometamol to impurity B Dissolve 1 mg of the substance to be examined in 1 mL of the mobile phase and heat the solution on a water-bath at 85 °C for 5 min and cool.

Reference solution (b) Dilute 2.0 mL of the test solution to 20.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent.

Mobile phase Dissolve 2.44 g of *sodium dihydrogen phosphate R* in *water R* and dilute to 1000 mL with *water R*; adjust to pH 2.5 with *phosphoric acid R* (about 0.6 mL); mix 770 mL of this solution with 230 mL of *acetonitrile R1*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 20 µL.

Run time 2.5 times the retention time of the principal peak (to elute degradation products formed during heating) for reference solution (a) and 10 min after the elution of dinoprost for the test solution and reference solution (b).

Retention time Impurity B = about 55 min; impurity A = about 60 min; dinoprost = about 66 min.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities B and A and minimum 2.0 between the peaks due to impurity A and dinoprost; if necessary, adjust the composition of the mobile phase by increasing the concentration of acetonitrile to decrease the retention times;

— *symmetry factor*: maximum 1.2 for the peaks due to impurities A and B.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity A*: not more than twice the area of the principal peak obtained with reference solution (b) (2 per cent);

— *impurities B, C, D*: for each impurity, not more than 1.5 times the area of the principal peak obtained with reference solution (b) (1.5 per cent) and not more than one such peak has an area greater than 0.5 times the area of the principal peak obtained with reference solution (b) (0.5 per cent);

— *sum of impurities other than A*: not more than twice the area of the principal peak obtained with reference solution (b) (2 per cent);

— *disregard limit*: 0.05 times the area of the principal peak obtained with reference solution (b) (0.05 per cent); disregard any peak due to trometamol (retention time = about 1.5 min).

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (23:77 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution Dissolve 10.0 mg of *dinoprost trometamol CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm) with a pore size of 10 nm and a carbon loading of 19 per cent.

Mobile phase Dissolve 2.44 g of *sodium dihydrogen phosphate R* in *water R* and dilute to 1000 mL with *water R*; adjust to pH 2.5 with *phosphoric acid R* (about 0.6 mL); mix 730 mL of this solution with 270 mL of *acetonitrile R1*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 200 nm.

Injection 20 µL.

Retention time Dinoprost = about 23 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 2.0 per cent for the peak due to dinoprost after 6 injections.

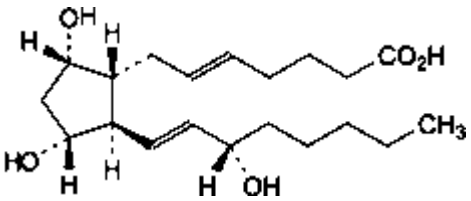
Calculate the percentage of dinoprost trometamol from the declared content of *dinoprost trometamol CRS*.

www.webofpharma.com

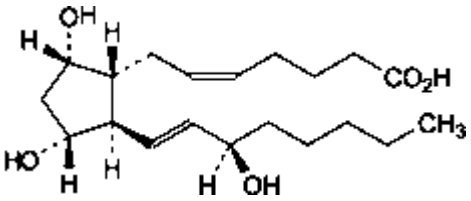
https://thuocngocanh.com/

IMPURITIES

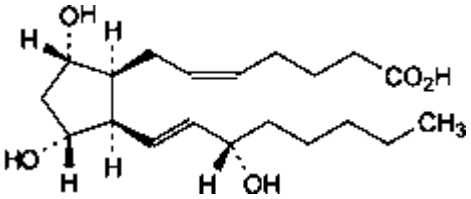
Specified impurities *A, B, C, D.*



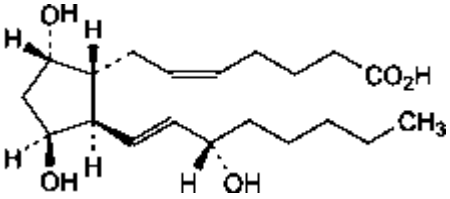
A. (*E*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid ((5*E*)-$PGF_{2\alpha}$; 5,6-*trans*-$PGF_{2\alpha}$),



B. (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-(3*R*)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid ((15*R*)-$PGF_{2\alpha}$;15-epi$PGF_{2\alpha}$),



C. (*Z*)-7-[(1*S*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid ((8*S*)-$PGF_{2\alpha}$; 8-epi$PGF_{2\alpha}$),



D. (*Z*)-7-[(1*R*,2*R*,3*S*,5*S*)-3,5-dihydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid (11β-$PGF_{2\alpha}$; 11-epi$PGF_{2\alpha}$).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

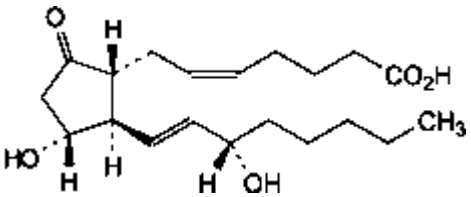
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Dinoprostone

General Notices

(Ph. Eur. monograph 1311)



$C_{20}H_{32}O_5$ 352.5 *363-24-6*

Action and use

Prostaglandin E_2(PGE_2); inducer of uterine muscle contraction.

Preparation

Dinoprostone Oral Solution

Ph Eur

DEFINITION

(*Z*)-7-[(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid (PGE_2).

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water, very soluble in methanol, freely soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

The substance degrades at room temperature.

IDENTIFICATION

A. Specific optical rotation (2.2.7): -90 to -82 (anhydrous substance).

Immediately before use, dissolve 50.0 mg in *alcohol R* and dilute to 10.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dinoprostone CRS*.

TESTS

Prepare the solutions immediately before use.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 10.0 mg of the substance to be examined in a 58 per cent *V/V* solution of *methanol R2* and dilute to 2.0 mL with the same solvent.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in a 58 per cent *V/V* solution of *methanol R2* and dilute to 20.0 mL with the same solvent.

Reference solution (a) Dissolve 1 mg of *dinoprostone CRS* and 1 mg of *dinoprostone impurity C CRS* in a 58 per cent *V/V* solution of *methanol R2* and dilute to 10.0 mL with the same solvent. Dilute 4.0 mL of the solution to 10.0 mL with a 58 per cent *V/V* solution of *methanol R2*.

Reference solution (b) Dilute 0.5 mL of test solution (a) to 10.0 mL with a 58 per cent *V/V* solution of *methanol R2*. Dilute 1.0 mL of the solution to 10.0 mL with a 58 per cent *V/V* solution of *methanol R2*.

Reference solution (c) In order to prepare *in situ* the degradation compounds (impurity D and impurity E), dissolve 1 mg of the substance to be examined in 100 µL of *1 M sodium hydroxide* (the solution becomes brownish-red), wait 4 min, add 150 µL of *dilute acetic acid R1* (yellowish-white opalescent solution) and dilute to 5.0 mL with a 58 per cent *V/V* solution of *methanol R2*.

Reference solution (d) Dissolve 20 mg of *dinoprostone CRS* in a 58 per cent *V/V* solution of *methanol R2* and dilute to 20.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R*,

— *temperature*: 30 °C.

Mobile phase Mix 42 volumes of a 0.2 per cent *V/V* solution of *acetic acid R* and 58 volumes of *methanol R2*.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL; inject test solution (a) and reference solutions (a), (b) and (c).

Relative retention With reference to dinoprostone (retention time = about 18 min): impurity C = about 1.2; impurity D = about 1.8; impurity E = about 2.0.

System suitability Reference solution (a):

— *resolution*: minimum of 3.8 between the peaks due to dinoprostone and to impurity C. If necessary adjust the concentration of the acetic acid solution and/or methanol (increase the concentration of the acetic acid solution to increase the retention time for dinoprostone and impurity C and increase the concentration of methanol to decrease the retention time for both compounds).

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.2; impurity E = 0.7,

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent),

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent),

— *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *total of other impurities*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent),

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

If any peak with a relative retention to dinoprostone of about 0.8 is greater than 0.5 per cent or if the total of other impurities is greater than 1.0 per cent, record the chromatogram of test solution (a) with a detector set at 230 nm. If the area of the peak at 230 nm is twice the area of the peak at 210 nm, multiply the area at 210 nm by 0.2 (correction factor for impurity F).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.50 g.

ASSAY

Prepare the solutions immediately before use.

Liquid chromatography (*2.2.29*) as described in the test for related substances.

www.webofpharma.com

https://thuocngocanh.com/

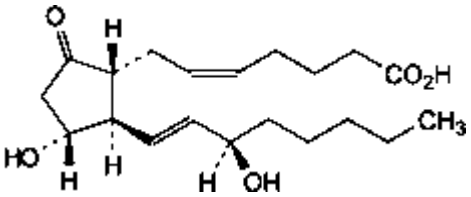
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{20}H_{32}O_5$.

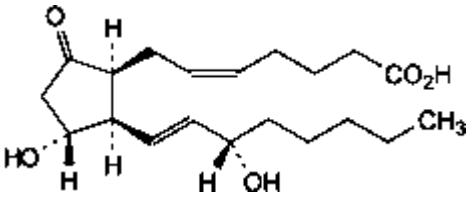
STORAGE

At a temperature not exceeding - 15 °C.

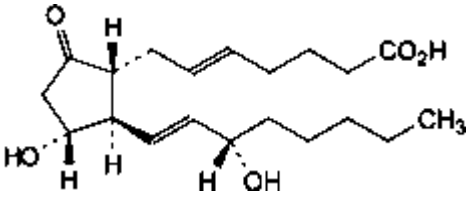
IMPURITIES



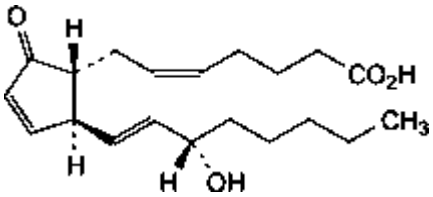
A. (*Z*)-7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*R*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid (15-epiPGE$_2$; (15*R*)-PGE$_2$),



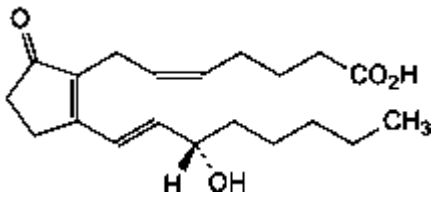
B. (*Z*)-7-[(1*S*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid (8-epiPGE$_2$; (8S)-PGE$_2$),



C. (*E*)-7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid (5-*trans*-PGE$_2$; (5*E*)-PGE$_2$),



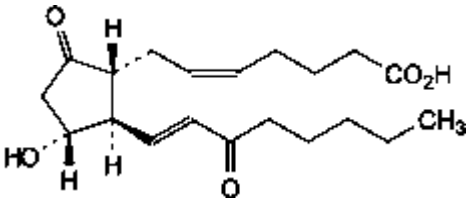
D. (*Z*)-7-[(1*R*,2*S*)-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopent-3-enyl]hept-5-enoic acid (PGA$_2$),



www.webofpharma.com

https://thuocngocanh.com/

E. (*Z*)-7-[2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopent-1-enyl]hept-5-enoic acid (PGB_2),



F. (*Z*)-7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-3-oxo-oct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid (15-oxo-PGE_2; 15-keto-PGE_2).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dinoprostone Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

DEFINITION

Dinoprostone Oral Solution is a solution of Dinoprostone in a suitable aqueous vehicle. It is intended to be diluted before use.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of dinoprostone, $C_{20}H_{32}O_5$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Evaporate about 20 mL of the oral solution to 15 mL under a stream of nitrogen, extract the remaining solution with two 5-mL quantities of *chloroform*, combine the chloroform extracts and evaporate almost to dryness using a rotary evaporator. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of dinoprostone (*RS 448*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Prostaglandin A_2

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be injected immediately after preparation.

(1) Dilute a quantity of the oral solution with sufficient *methanol (60%)* to produce a solution containing 0.01% w/v of Dinoprostone.

(2) Dilute 1 volume of solution (1) to 10 volumes with *methanol (60%)* and further dilute 1 volume to 10 volumes with *methanol (60%)*.

(3) Dissolve 1 mg of *dinoprostone EPCRS* in 100 µL of 1M *sodium hydroxide* (the solution becomes brownish-red), allow to stand for 4 minutes and then add 150 µL of 1M *acetic acid* (a yellowish-white opalescent solution is produced). Dilute the resulting solution to 5 mL with *methanol (60%)* and further dilute 1 mL of this solution to 10 mL with *methanol (60%)*. The solution contains a mixture of prostaglandin A_2 (Ph. Eur. impurity D) and prostaglandin B_2 (Ph. Eur. impurity E).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

40 volumes of a 1% v/v solution of *triethylamine*, adjusted to pH 2.3 with *orthophosphoric acid*, and 60 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of dinoprostone is about 22 minutes. The retention times relative to dinoprostone are: impurity D, about 1.7; impurity E, about 1.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to prostaglandin A_2 using solution (3) and multiply the area of this peak by the corresponding correction factor: 0.2;

the area of any peak corresponding to prostaglandin A_2 is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be injected immediately after preparation.

(1) Dilute a quantity of the oral solution with sufficient *methanol (60%)* to produce a solution containing 0.01% w/v of Dinoprostone.

(2) Dissolve 10 mg of *dinoprostone EPCRS* *in* *methanol (60%)* with the aid of ultrasound for 5 minutes and dilute to 100 mL with *methanol (60%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the test for Prostaglandin A_2 may be used, but injecting 20 µL of each solution.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{20}H_{32}O_5$, weight in volume, using the declared content of $C_{20}H_{32}O_5$ in *dinoprostone EPCRS*.

STORAGE

Dinoprostone Oral Solution should be protected from light and stored at a temperature of 2° to 8°.

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

The label states (1) that the preparation is to be diluted before use; (2) that any oral solution not used within 7 days of the date of preparation should be discarded.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

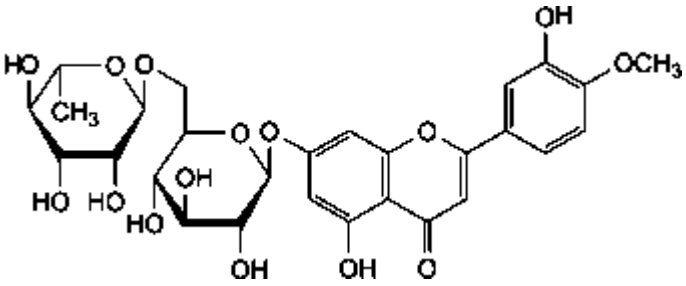
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diosmin

General Notices

(Ph. Eur. monograph 1611)



$C_{28}H_{32}O_{15}$ 609 *520-27-4*

Action and use

Chronic venous insufficiency (flavonoid).

Ph Eur

DEFINITION

7-[[6-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one.

Substance obtained through iodine-assisted oxidation of (2*S*)-7-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (hesperidin) of natural origin.

Content 90.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Greyish-yellow or light yellow, hygroscopic powder.

Solubility

Practically insoluble in water, soluble in dimethyl sulfoxide, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison diosmin CRS.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Iodine

Maximum 0.1 per cent.

Determine the total content of iodine by potentiometry, using an iodide-selective electrode (2.2.36), after oxygen combustion (2.5.10).

Test solution Wrap 0.100 g of the substance to be examined in a piece of filter paper and place it in a sample carrier. Introduce into the flask 50 mL of a 0.2 g/L solution of hydrazine R. Flush the flask with oxygen for 10 min. Ignite the filter paper. Stir the contents of the flask immediately after the end of the combustion to dissolve completely the combustion products. Continue stirring for 1 h.

Reference solution Dilute 2.0 mL of a 16.6 g/L solution of potassium iodide R to 100.0 mL with water R. Dilute 10.0 mL of this solution to 100.0 mL with water R.

Introduce into a beaker 30 mL of a 200 g/L solution of potassium nitrate R in 0.1 M nitric acid. Immerse the electrodes and stir for 10 min. The potential of the solution (nT_1) must remain stable. Add 1 mL of the test solution and measure the potential (nT_2).

Introduce into a beaker 30 mL of a 200 g/L solution of potassium nitrate R in 0.1 M nitric acid. Immerse the electrodes and stir for 10 min. The potential of the solution must remain stable (nR_1). Add 80 µL of the reference solution and measure the potential (nR_2).

The absolute value $|nT_2 - nT_1|$ is not higher than the absolute value $|nR_2 - nR_1|$.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in dimethyl sulfoxide R and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 25.0 mg of diosmin CRS in dimethyl sulfoxide R and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with dimethyl sulfoxide R.

Reference solution (c) Dissolve 5.0 mg of diosmin for system suitability CRS (containing impurities A, B, C, D, E and F) in dimethyl sulfoxide R and dilute to 5.0 mL with the same solvent.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, *glacial acetic acid R*, *methanol R*, *water R* (2:6:28:66 *V/V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time 6 times the retention time of diosmin.

Identification of impurities Use the chromatogram supplied with *diosmin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention With reference to diosmin (retention time = about 4 min): impurity A = about 0.5; impurity B = about 0.6; impurity C = about 0.8; impurity D = about 2.2; impurity E = about 2.6; impurity F = about 4.5.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to impurities B and C.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.4; impurity F = 0.6;

— for each impurity, use the concentration of diosmin in reference solution (b).

Limits:

— *impurity B*: maximum 4.0 per cent;

— *impurities C, E*: for each impurity, maximum 3.0 per cent;

— *impurity F*: maximum 2.0 per cent;

— *impurity D*: maximum 0.6 per cent;

— *impurity A*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.4 per cent;

— *total*: maximum 8.5 per cent;

— *reporting threshold*: 0.10 per cent.

www.webofpharma.com

https://thuocngocanh.com/

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Water (*2.5.12*)

Maximum 6.0 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{28}H_{32}O_{15}$ taking into account the assigned content of *diosmin CRS*.

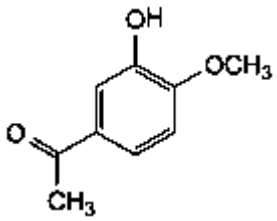
STORAGE

In an airtight container.

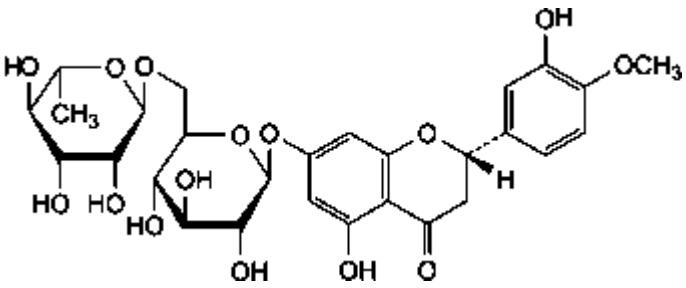
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G.*



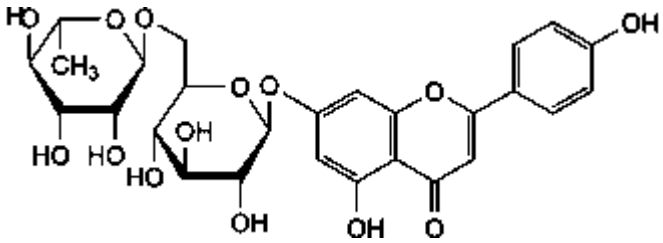
A. 1-(3-hydroxy-4-methoxyphenyl)ethan-1-one (acetoisovanillone),



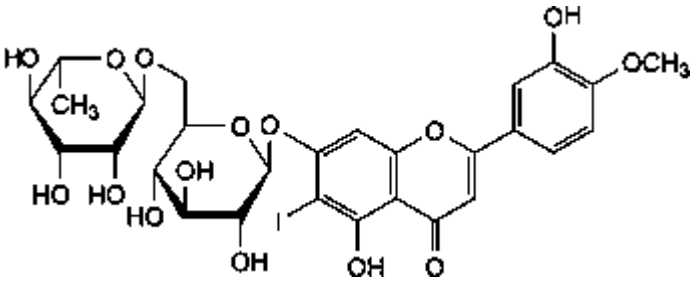
www.webofpharma.com

https://thuocngocanh.com/

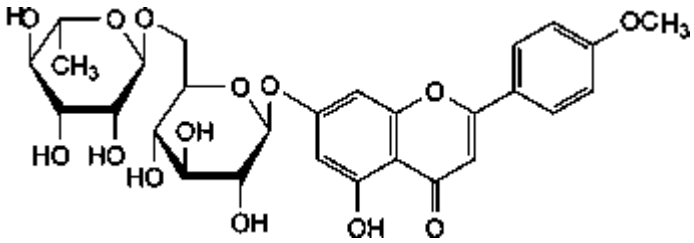
B. (2*S*)-7-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (hesperidin),



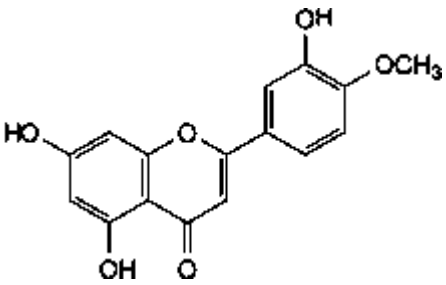
C. 7-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one (isorhoifolin),



D. 7-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-6-iodo-4*H*-1-benzopyran-4-one (6-iododiosmin),



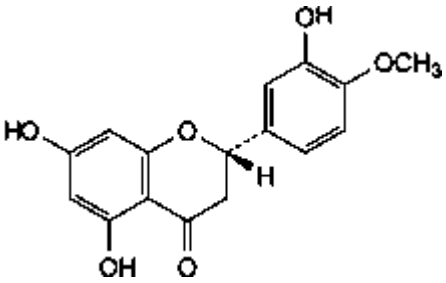
E. 7-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-5-hydroxy-2-(4-methoxyphenyl)-4*H*-1-benzopyran-4-one (linarin),



F. 5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one (diosmetin),

www.webofpharma.com

https://thuocngocanh.com/



G. (2*S*)-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (hesperetin).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

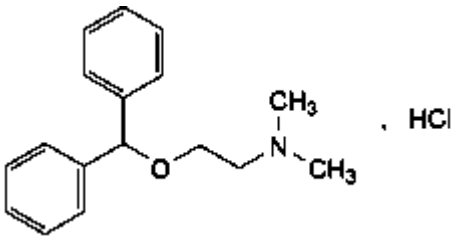
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diphenhydramine Hydrochloride

General Notices

(Ph. Eur. monograph 0023)



$C_{17}H_{22}ClNO$ 291.8 *147-24-0*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Preparations

Diphenhydramine Oral Solution

Diphenhydramine Tablets

Ph Eur

DEFINITION

2-(Diphenylmethoxy)-*N*,*N*-dimethylethanamine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: C, D.

Second identification: A, B, D.

A. Melting point (2.2.14): 168 °C to 172 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50 mg in ethanol (96 per cent) R and dilute to 100.0 mL with the same solvent.

Spectral range 230-350 nm.

Absorption maxima At 253 nm, 258 nm and 264 nm.

Absorbance ratios:

— A_{258}/A_{253} = 1.1 to 1.3;

— A_{258}/A_{264} = 1.2 to 1.4.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison diphenhydramine hydrochloride CRS.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.0 g in carbon dioxide-free water R and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S and a fivefold dilution of solution S are clear (2.2.1). Solution S is not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Acidity or alkalinity

To 10 mL of solution S add 0.15 mL of methyl red solution R and 0.25 mL of 0.01 M hydrochloric acid. The solution is pink. Not more than 0.5 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 70 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 10.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *diphenhydramine impurity A CRS* and 5 mg of *diphenylmethanol R* in the mobile phase and dilute to 10.0 mL with the mobile phase. To 2.0 mL of this solution add 1.5 mL of the test solution and dilute to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of a 5.4 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 using *phosphoric acid R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time 7 times the retention time of diphenhydramine.

Relative retention With reference to diphenhydramine (retention time = about 6 min): impurity A = about 0.9; impurity B = about 1.5; impurity C = about 1.8; impurity D = about 2.6; impurity E = about 5.1.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to diphenhydramine and to impurity A.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity D by 0.7,

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *any other impurity*: not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

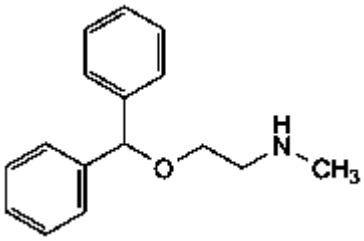
1 mL of *0.1 M sodium hydroxide* is equivalent to 29.18 mg of $C_{17}H_{22}ClNO$.

STORAGE

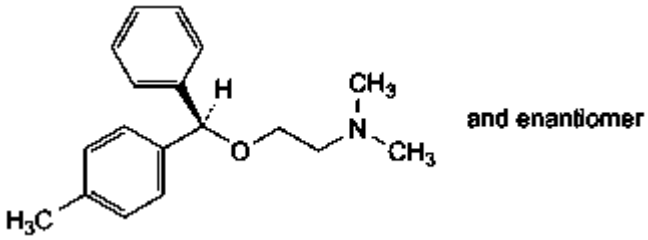
Protected from light.

IMPURITIES

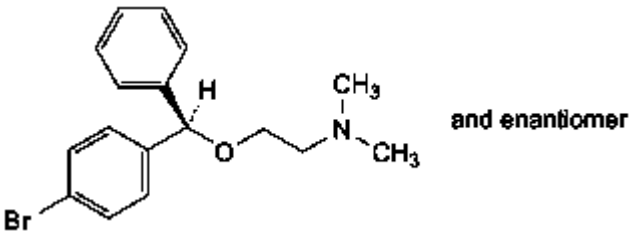
Specified impurities *A, B, C, D, E.*



A. 2-(diphenylmethoxy)-*N*-methylethanamine,



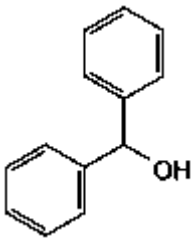
B. 2-[(*RS*)-(4-methylphenyl)phenylmethoxy]-*N,N*-dimethylethanamine,



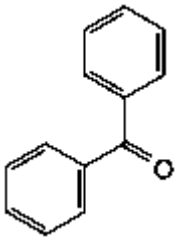
C. 2-[(*RS*)-(4-bromophenyl)phenylmethoxy]-*N,N*-dimethylethanamine,

www.webofpharma.com

https://thuocngocanh.com/



D. diphenylmethanol (benzhydrol),



E. diphenylmethanone (benzophenone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diphenhydramine Oral Solution

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Diphenhydramine Oral Solution is a solution of Diphenhydramine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of diphenhydramine hydrochloride, $C_{17}H_{21}NO,HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 50 volumes of *ethanol (96%)*, 30 volumes of *glacial acetic acid* and 20 volumes of *water* as the mobile phase. Apply separately to the plate 5 µL of each of the following freshly prepared solutions. For solution (1) acidify a quantity of the oral solution containing 50 mg of diphenhydramine hydrochloride with *2M hydrochloric acid*, shake with three 20 mL quantities of *ether*, discard the ether, extract with two 20 mL quantities of *chloroform*, dry the combined extracts over *anhydrous sodium sulfate*, filter, evaporate the chloroform and dissolve the cooled residue in 5 mL of *chloroform*. Solution (2) contains 1% w/v of *diphenhydramine hydrochloride BPCRS* in *chloroform*. After removal of the plate, allow it to dry in air and spray with a solution containing 0.25% w/v of *chloroplatinic(IV) acid* and 5% w/v of *potassium iodide*. The principal spot in the chromatogram obtained with solution (1) corresponds in colour and position to that in the chromatogram obtained with solution (2).

B. Evaporate to dryness 1 mL of solution (1) obtained in test A, dissolve the residue in 0.15 mL of *water* and add 2 mL of *sulfuric acid*; a yellow colour is produced which, on the addition of 0.5 mL of *nitric acid*, changes to red. Add 15 mL of *water*, cool, add 5 mL of *chloroform*, shake and allow to separate; the chloroform layer is violet.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel H* as the coating substance and a mixture of 80 volumes of *chloroform* and 20 volumes of *methanol* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) use solution (1) described under test A for Identification. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *chloroform*. After removal of the plate, allow it to dry in air and spray with *dilute potassium iodobismuthate solution*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

ASSAY

www.webofpharma.com

https://thuvienthuocngocanh.com/

Acidify a quantity containing 0.1 g of diphenhydramine hydrochloride with *2M hydrochloric acid*, shake with three 20 mL quantities of *ether*, discard the ether, make the aqueous solution alkaline with 5M *sodium hydroxide* and extract with successive 15 mL quantities of *ether* until extraction is complete. Wash the combined ether extracts with two 5 mL quantities of *water*, extract the combined washings with 15 mL of *ether* and evaporate the combined ether extracts to dryness. Dissolve the residue in 15 mL of *0.05M sulfuric acid VS* and titrate the excess of acid with *0.1M sodium hydroxide VS* using *methyl red solution* as indicator. Each mL of *0.05M sulfuric acid VS* is equivalent to 29.18 mg of $C_{17}H_{21}NO,HCl$.

STORAGE

Diphenhydramine Oral Solution should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diphenhydramine Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Diphenhydramine Tablets contain Diphenhydramine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diphenhydramine hydrochloride, $C_{17}H_{21}NO,HCl$

95.0 to 105.0% of the stated amount.

Carry out all of the following procedures protected from light.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Diphenhydramine Hydrochloride with 50 mL of *ethanol*, centrifuge and filter the supernatant liquid. Evaporate the filtrate to dryness under a stream of nitrogen and dry the residue at 105° for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of diphenhydramine hydrochloride *(RS 450)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, and rotate the basket at 100 revolutions per minute.

(b) Use 500 mL of *mixed phosphate buffer pH 6.8*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 25 mL sample of the medium and measure the *absorbance* of the filtered sample (a 0.45µm filter is suitable), suitably diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.005% w/v of Diphenhydramine Hydrochloride, at the maximum at 254 nm, Appendix II B, using *mixed phosphate buffer pH 6.8* in the reference cell.

(2) Measure the *absorbance* of a 0.005% w/v solution of *diphenhydramine hydrochloride BPCRS* using *mixed phosphate buffer pH 6.8* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thietbiuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of diphenhydramine hydrochloride, $C_{17}H_{21}NO,HCl$, in the medium from the absorbances obtained and using the declared content of $C_{17}H_{21}NO,HCl$ in *diphenhydramine hydrochloride BPCRS*.

LIMITS

The amount of diphenhydramine hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the powdered tablets containing 70 mg of Diphenhydramine Hydrochloride in 20 mL of the mobile phase. Dilute 1 volume to 5 volumes with the mobile phase.
(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.
(3) Dissolve 5 mg of *diphenhydramine impurity A EPCRS* and 5 mg of *diphenylmethanol* in the mobile phase and dilute to 10 mL with the mobile phase. To 4 volumes of this solution add 3 volumes of solution (1) and dilute to 20 volumes with the mobile phase.
(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated octylsilyl silica gel for chromatography* (5µm) (Lichrospher RP Select B is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for 7 times the retention time of the peak due to diphenhydramine.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of a 0.54% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 using *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to diphenhydramine (retention time = about 6 minutes) are: impurity A = about 0.9; impurity B = about 1.5; impurity C = about 1.8; impurity D = about 2.6; impurity E = about 5.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to diphenhydramine and impurity A is at least 2.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity D and multiply the area of this peak by a correction factor of 0.7.

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B, C, D or E is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix for 10 minutes, with the aid of ultrasound, a quantity of the powdered tablets containing 50 mg of Diphenhydramine Hydrochloride with 50 mL of *water*, add sufficient *water* to produce 100 mL, mix and filter, use the filtrate.
(2) 0.05% w/v *diphenhydramine hydrochloride BPCRS*.
(3) Dissolve 5 mg of *benzophenone* in 5 mL of *acetonitrile;* add sufficient water to produce 100 mL. To 1 mL of this solution add 5 mg of *diphenhydramine hydrochloride BPCRS* and add sufficient *water* to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (5µm).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

1 volume of *triethylamine*, 60 volumes of *acetonitrile* and 140 volumes of *water* adjusted to pH 5.5 using *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to benzophenone and diphenhydramine is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{21}NO,HCl$ in the tablets using the declared content of $C_{17}H_{21}NO,HCl$ in *diphenhydramine hydrochloride BPCRS*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

STORAGE

Diphenhydramine Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Diphenhydramine Hydrochloride.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

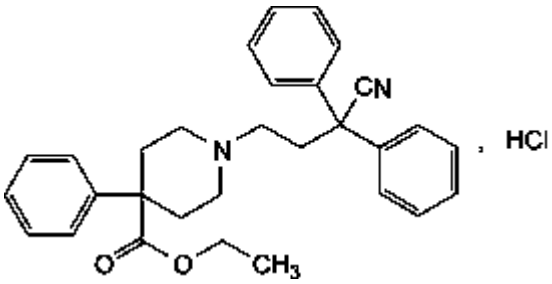
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diphenoxylate Hydrochloride

General Notices

(Ph. Eur. monograph 0819)



$C_{30}H_{33}ClN_2O_2$ 489.1 *3810-80-8*

Action and use

Opioid receptor agonist; treatment of diarrhoea.

Ph Eur

DEFINITION

Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *diphenoxylate hydrochloride CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Dissolve about 30 mg in 5 mL of *methanol R*. Add 0.25 mL of *nitric acid R* and 0.4 mL of *silver nitrate solution R1*. Shake and allow to stand. A curdled precipitate is formed. Centrifuge and rinse the precipitate with 3 quantities, each of 2 mL, of *methanol R*. Carry out this operation rapidly and protected from bright light. Suspend the precipitate in 2 mL of *water R* and add 1.5 mL of *ammonia R*. The precipitate dissolves easily.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 1.0 g in *methylene chloride R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solution A Adjust 900 mL of *water R* to pH 2.3 with *phosphoric acid R* and dilute to 1000.0 mL with *water R*.

Solvent mixture *acetonitrile R1*, solution A (50:50 *V/V*).

Test solution Dissolve 25 mg of the substance to be examined in 20 mL of the solvent mixture, sonicate for 2 min, cool and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2 mg of *diphenoxylate for system suitability CRS* (containing impurity A) in 2.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: solution A;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	75	25
5 - 40	75 → 15	25 → 85

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Relative retention With reference to diphenoxylate (retention time = about 16 min): impurity A = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and diphenoxylate.

Limits:

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 40 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M ethanolic sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M ethanolic sodium hydroxide* is equivalent to 48.91 mg of $C_{30}H_{33}ClN_2O_2$.

STORAGE

Protected from light.

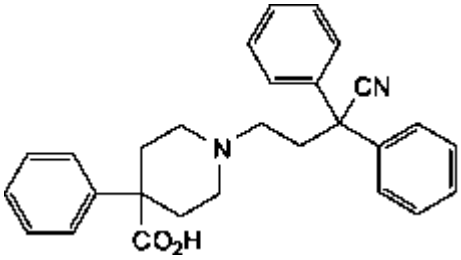
IMPURITIES

Specified impurities *A*.

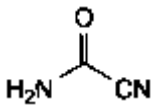
www.webofpharma.com

https://thuocngocanh.com/

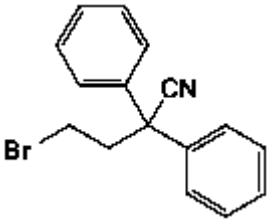
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.



A. 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid (diphenoxylic acid),



B. 1-cyanomethanamide,



C. 4-bromo-2,2-diphenylbutanenitrile.

Ph Eur

© Crown Copyright 2022

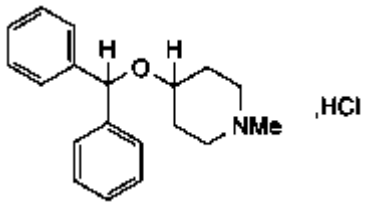
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diphenylpyraline Hydrochloride

General Notices



$C_{19}H_{23}NO,HCl$ 317.9 *132-18-3*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Diphenylpyraline Hydrochloride is 4-benzhydryloxy-1-methylpiperidine hydrochloride. It contains not less than 98.0% and not more than 101.0% of $C_{19}H_{23}NO,HCl$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white powder; odourless or almost odourless.

Freely soluble in *water* and in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of diphenylpyraline hydrochloride *(RS 106)*.

B. Yields the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Dissolve 45 mg of *bibenzyl* (internal standard) in sufficient *dichloromethane* to produce 100 mL.

(2) Dissolve 0.20 g of the substance being examined in 20 mL of *water*, make the solution alkaline with 5M *ammonia* and extract with three 25-mL quantities of *dichloromethane*. Shake the combined extracts with 10 g of *anhydrous sodium sulfate*, filter, evaporate the filtrate to dryness at about 30° and dissolve the residue in 2 mL of *dichloromethane*.

www.webofpharma.com

https://thuocngocanh.com/

(3) Prepare solution (3) in the same manner as solution (2) but dissolve the residue in 2 mL of solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m×4 mm) packed with *silanised diatomaceous support* (80 to 100 mesh) coated with 3% w/w of phenyl methyl silicone fluid (50% phenyl) (OV-17 is suitable).

(b) Use *nitrogen* as the carrier gas.

(c) Use an oven temperature of 165°. Allow the chromatography to proceed for 3 times the retention time of bibenzyl.

(d) Increase the oven temperature to 240° to elute the diphenylpyraline from the column.

LIMITS

In the chromatogram obtained with solution (3):

the sum of the areas of any *secondary peaks* is not greater than the area of the peak due to the internal standard.

Loss on drying

When dried to constant weight at 105°, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.2 g, adding 5 mL of *mercury(II) acetate solution* and determining the end-point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 31.79 mg of $C_{19}H_{23}NO,HCl$.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

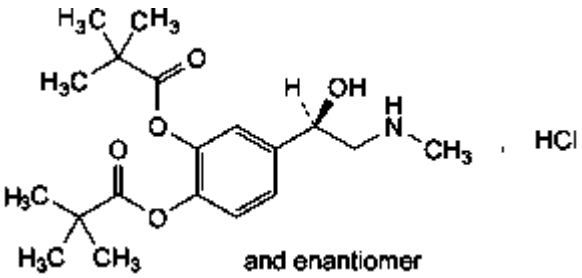
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipivefrine Hydrochloride

General Notices

(Ph. Eur. monograph 1719)



$C_{19}H_{30}ClNO_5$ 387.9 *64019-93-8*

Action and use

Adrenaline prodrug; treatment of glaucoma.

Ph Eur

DEFINITION

Hydrochloride of 4-[(1*RS*)-1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate).

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very soluble in methanol, freely soluble in ethanol (96 per cent) and in methylene chloride.

mp

About 160 °C.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *dipivefrine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Impurities A and B

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *0.01 M hydrochloric acid* and dilute to 10.0 mL with the same acid.

Reference solution Dissolve 10.0 mg of *adrenaline R* and 10.0 mg of *adrenalone hydrochloride R* in *0.01 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 1.0 mL of this solution to 10.0 mL with *0.01 M hydrochloric acid*. *Protect this solution from light*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm).

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *anhydrous formic acid R*;

— *mobile phase B*: *methanol R2*, *acetonitrile R* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 5	100 → 40	0 → 60
5 - 10	40	60

Flow rate 1 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 10 µL.

Retention times Impurity A = about 2.2 min; impurity B = about 3.2 min.

System suitability Reference solution:

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mix 40 volumes of *methanol R2* and 60 volumes of *acetonitrile R*. Mix 55 volumes of this mixture and 45 volumes of *0.01 M hydrochloric acid*.

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *dipivefrine for system suitability CRS* (containing impurities C, D and E) in the solvent mixture and dilute to 2.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of *dipivefrine hydrochloride CRS* in the solvent mixture and dilute to 2.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm).

Mobile phase Mix 45 volumes of a 2.7 g/L solution of *concentrated ammonia R* adjusted to pH 10.0 with *dilute acetic acid R* and 55 volumes of a mixture of 40 volumes of *methanol R2* and 60 volumes of *acetonitrile R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 10 µL.

Run time 2.5 times the retention time of dipivefrine.

Relative retention With reference to dipivefrine (retention time = about 7 min): impurities C and D = about 0.4; impurity E = about 1.3; impurity F = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to dipivefrine and impurity E.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurities C and D = 0.5; impurity E = 0.06;

— *sum of impurities C and D*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities E, F*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak with a mass distribution ratio less than 0.5.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 6 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 20 µL of reference solutions (a) and (c).

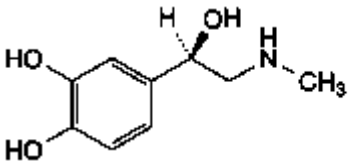
System suitability Reference solution (c):

— *symmetry factor*: maximum 2.0 for the peak due to dipivefrine.

Calculate the percentage content of $C_{19}H_{30}ClNO_5$ using the chromatograms obtained with reference solutions (a) and (c) and the declared content of *dipivefrine hydrochloride CRS*.

IMPURITIES

Specified impurities *A, B, C, D, E, F.*

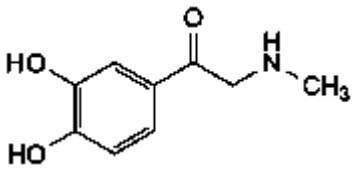


and enantiomer

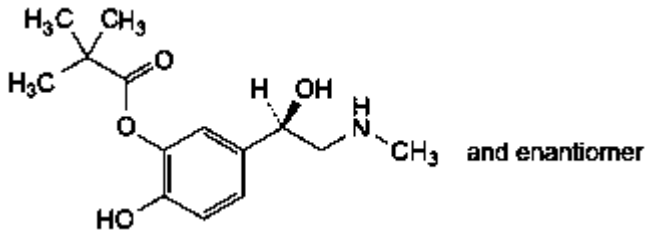
www.webofpharma.com

https://thuocngocanh.com/

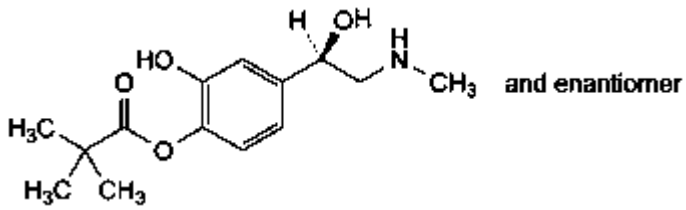
A. 4-[(1*RS*)-1-hydroxy-2-(methylamino)ethyl]benzene-1,2-diol ((±)-adrenaline),



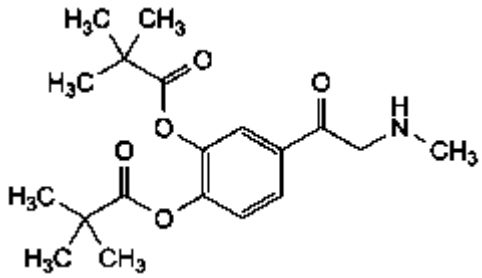
B. 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanone (adrenalone),



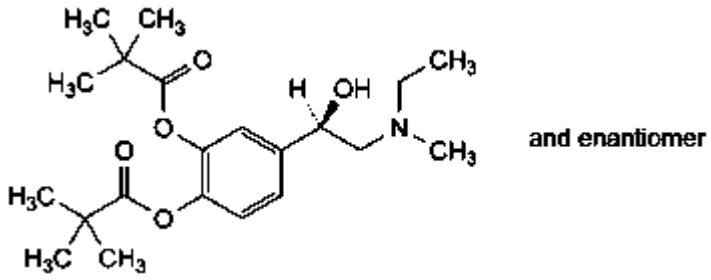
C. 2-hydroxy-5-[(1*RS*)-1-hydroxy-2-(methylamino)ethyl]phenyl 2,2-dimethylpropanoate,



D. 2-hydroxy-4-[(1*RS*)-1-hydroxy-2-(methylamino)ethyl]phenyl 2,2-dimethylpropanoate,



E. 4-[(methylamino)acetyl]-1,2-phenylene bis(2,2-dimethylpropanoate) (adrenalone dipivalate ester),



F. 4-[(1*RS*)-2-(ethylmethylamino)-1-hydroxyethyl]-1,2-phenylene bis(2,2-dimethylpropanoate).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

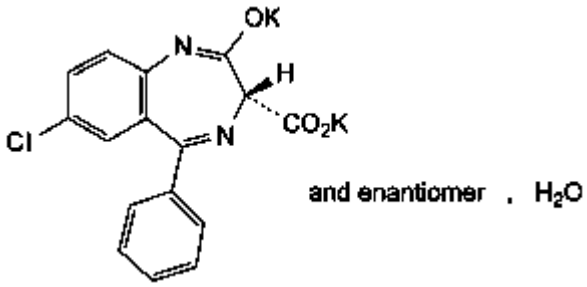
Dipotassium Clorazepate Monohydrate

General Notices

Dipotassium Clorazepate

Potassium Clorazepate

(Ph. Eur. monograph 0898)



$C_{16}H_9ClK_2N_2O_3,H_2O$ 408.9

Action and use

Hypnotic; anxiolytic.

Ph Eur

DEFINITION

Dipotassium (3*RS*)-7-chloro-2-oxido-5-phenyl-3*H*-1,4-benzodiazepine-3-carboxylate monohydrate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or light yellow, crystalline powder, hygroscopic.

Solubility

Freely soluble to very soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

Solutions in water and in ethanol (96 per cent) are unstable and are to be used immediately.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs, if the reference spectrum is used for comparison.

Comparison *dipotassium clorazepate monohydrate CRS* or *Ph. Eur. reference spectrum of dipotassium clorazepate monohydrate*.

B. Place 1.0 g in a crucible and add 2 mL of *dilute sulfuric acid R*. Heat on a water-bath, then ignite until all black particles have disappeared. Allow to cool. Take up the residue with *water R* and dilute to 20 mL with the same solvent. The solution gives reaction (b) of potassium (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution GY_5 (2.2.2, *Method II*).

Rapidly dissolve 2.0 g with shaking in *water R* and dilute to 20.0 mL with the same solvent. Observe immediately.

Impurity B

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solutions (a) and (c).

Calculation of percentage content:

— *correction factor*: multiply the peak area of impurity B by 0.6;

— use the concentration of dipotassium clorazepate monohydrate in reference solution (a).

Limit:

— *impurity B*: maximum 0.2 per cent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solution A Dissolve 11.7 g of *dipotassium hydrogen phosphate R* in about 900 mL of *water R*, adjust to pH 7.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*. Mix equal volumes of this solution and *methanol R*.

Solution B *methanol R*, 20 g/L solution of *potassium carbonate R* (30:70 *V/V*).

Test solution (a) Dissolve 10.0 mg of the substance to be examined in solution A and dilute to 20.0 mL with solution A.

Test solution (b) Dissolve 10.0 mg of the substance to be examined in solution B cooled to 0 °C and dilute to 20.0 mL with solution B.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 10 mg of *aminochlorobenzophenone R* (impurity A) and 10 mg of *ethyl clorazepate R* (impurity C) in *methanol R* and dilute to 200 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *methanol R*.

Reference solution (c) Dissolve 15 mg of *nordazepam R* (impurity B) in *methanol R* and dilute to 20 mL with the same solvent. Dilute 1 mL of the solution to 20 mL with solution B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 28 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.17 g of *dipotassium hydrogen phosphate R* in about 580 mL of *water for chromatography R*, adjust to pH 8.0 with *phosphoric acid R*, dilute to 650 mL with *water for chromatography R*, and add 450 mL of *methanol R1*;

— *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 20	80 → 50	20 → 50
20 - 25	50	50

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 230 nm.

Autosampler Set at 4 °C.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

Relative retention With reference to clorazepate (retention time = about 3 min): impurity B = about 4.6; impurity C = about 6.2; impurity A = about 6.5.

System suitability Reference solution (b):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 1.8 between the peaks due to impurities C and A.

Calculation of percentage contents:

— for each impurity, use the concentration of dipotassium clorazepate monohydrate in reference solution (a).

Limits:

— *impurity C*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to impurity B.

Water (*2.5.12*)

3.5 per cent to 5.5 per cent, determined on 0.250 g.

ASSAY

Dissolve 0.130 g in 10 mL of *anhydrous acetic acid R*. Add 30 mL of *methylene chloride R*. Titrate with *0.1 M perchloric acid*, determining the 2 points of inflexion by potentiometry (*2.2.20*).

At the 2nd point of inflexion, 1 mL of *0.1 M perchloric acid* is equivalent to 13.03 mg of $C_{16}H_9ClK_2N_2O_3$.

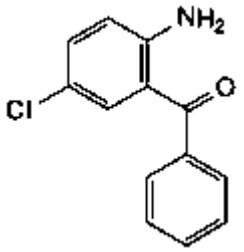
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities B, C.

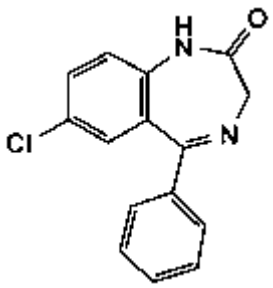
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



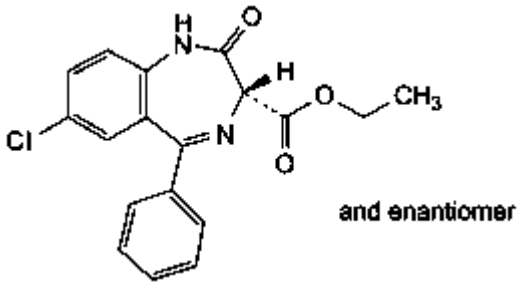
www.webofpharma.com

https://thuvienthuocngocanh.com/

A. (2-amino-5-chlorophenyl)phenylmethanone (aminochlorobenzophenone),



B. 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (nordazepam),



C. ethyl (3*RS*)-7-chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine-3-carboxylate (ethyl clorazepate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipotassium Hydrogen Phosphate

General Notices

(Dipotassium Phosphate, Ph. Eur. monograph 1003)

K_2HPO_4 174.2 *7758-11-4*

Action and use

Excipient.

Preparation

Dipotassium Hydrogen Phosphate Injection

Ph Eur

DEFINITION

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or colourless crystals, very hygroscopic.

Solubility

Very soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly alkaline (*2.2.4*).

B. Solution S gives reaction (b) of phosphates (*2.3.1*).

C. Solution S gives reaction (a) of potassium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *distilled water R* and dilute to 50 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Reducing substances

To 5 mL of solution S add 5 mL of *dilute sulfuric acid R* and 0.25 mL of a 3.2 g/L solution of *potassium permanganate R* and heat on a water-bath for 5 min. The solution remains faintly pink.

Monopotassium phosphate

Maximum 2.5 per cent.

From the volumes of *1 M sodium hydroxide* (n_1 mL, n_2 mL and n_3 mL) used in the assay, calculate the following ratio:

$$\frac{n_2 - n_3}{n_3 - n_1}$$

This ratio is not greater than 0.025.

Chlorides (*2.4.4*)

Maximum 200 ppm.

To 2.5 mL of solution S add 10 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.1 per cent.

To 1.5 mL of solution S add 2 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Sodium

Maximum 0.1 per cent, if intended for use in the manufacture of parenteral preparations.

Atomic emission spectrometry (*2.2.22, Method I*).

Test solution Dissolve 1.00 g in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*, diluted as necessary with *water R*.

Wavelength 589 nm.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 125-130 °C.

www.webofpharma.com

https://thuocngocanh.com/

Bacterial endotoxins (*2.6.14*)

Less than 1.1 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 0.800 g (*m*) in 40 mL of *carbon dioxide-free water R* and add 10.0 mL of *1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*) using *1 M sodium hydroxide*. Read the volume added at the 1st inflexion point (n_1 mL). Continue the titration to the 2nd inflexion point (total volume of *1 M sodium hydroxide* required, n_2 mL). Carry out a blank titration (n_3 mL).

Calculate the percentage content of K_2HPO_4 from the following expression:

$$\frac{1742\left(n_3 - n_1\right)}{m\left(100 - d\right)}$$

d = percentage loss on drying.

STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipotassium Hydrogen Phosphate Injection

General Notices

Dipotassium Phosphate Injection

DEFINITION

Dipotassium Hydrogen Phosphate Injection is a sterile solution of Dipotassium Hydrogen Phosphate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of dipotassium hydrogen phosphate, K_2HPO_4

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Yields the reactions characteristic of *potassium salts* and reaction B characteristic of *phosphates*, Appendix VI.

TESTS

Alkalinity

pH, 9.0 to 10.0, Appendix V L.

ASSAY

Dilute, if necessary, a volume of the injection with sufficient *carbon dioxide-free water* to produce a solution containing 8.71% w/v (1 millimole of potassium ion per mL) of dipotassium hydrogen phosphate. Titrate 20 mL with *0.5M hydrochloric acid VS* using a mixture of 4 volumes of *bromocresol green solution* and 1 volume of *methyl red solution* as indicator. Each mL of *0.5M hydrochloric acid VS* is equivalent to 87.1 mg of K_2HPO_4.

LABELLING

The label states (1) the percentage w/v of Dipotassium Phosphate; (2) the concentration of the potassium ion in millimoles.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

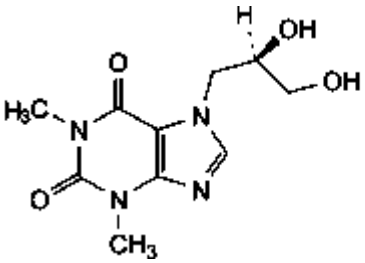
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diprophylline

General Notices

(Ph. Eur. monograph 0486)



and enantiomer

$C_{10}H_{14}N_4O_4$ 254.2 *479-18-5*

Action and use

Non-selective phosphodiesterase inhibitor (xanthine); treatment of reversible airways obstruction.

Ph Eur

DEFINITION

7-[(2*RS*)-2,3-Dihydroxypropyl]-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison: *diprophylline CRS*.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.25 mL of *bromothymol blue solution R1*. The solution is yellow or green. Not more than 0.4 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 5 mg of *etofylline CRS* (impurity C) in *water R* and dilute to 50 mL with the same solvent. Dilute 0.5 mL of the solution to 20 mL with the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R* (3 µm);

— *temperature*: 30 °C.

Mobile phase *methanol R*, *water for chromatography R* (10:90 *V/V*).

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 10 µL.

Run time 3 times the retention time of diprophylline.

Relative retention With reference to diprophylline (retention time = about 18 min): impurity C = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to diprophylline.

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (2.4.4)

Maximum 400 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.200 g in 3.0 mL of *anhydrous formic acid R* and add 50.0 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 25.42 mg of $C_{10}H_{14}N_4O_4$.

STORAGE

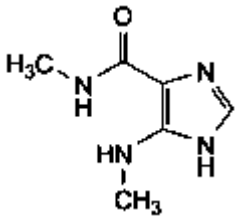
Protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D.

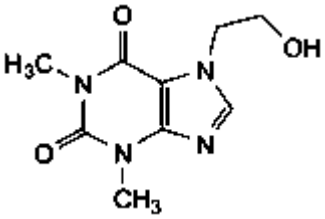
www.webofpharma.com

https://thuocngocanh.com/

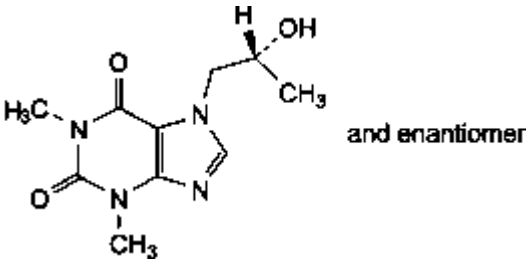


A. *N*-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide (theophyllidine),

B. 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theophylline),



C. 7-(2-hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (etofylline),



D. 7-[(2*RS*)-2-hydroxypropyl]-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (proxyphylline).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

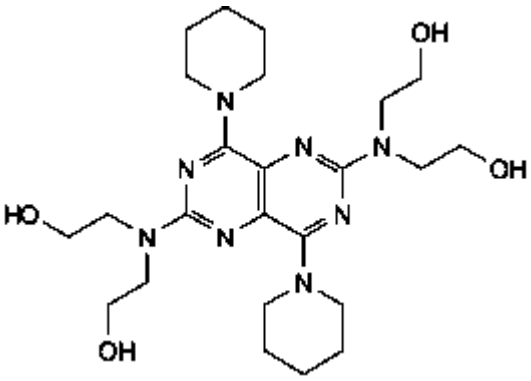
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipyridamole

General Notices

(Ph. Eur. monograph 1199)



$C_{24}H_{40}N_8O_4$ 504.6 *58-32-2*

Action and use

Adenosine reuptake inhibitor; inhibitor of platelet aggregation.

Preparations

Dipyridamole Prolonged-release Capsules

Dipyridamole Infusion

Dipyridamole Oral Suspension

Dipyridamole Tablets

Ph Eur

DEFINITION

2,2′,2″,2‴-[[4,8-Di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine-2,6-diyl]dinitrilo]tetraethanol.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

Bright yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in anhydrous ethanol. It dissolves in dilute mineral acids.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Preparation Discs of *potassium bromide R*.

Comparison *dipyridamole CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 50 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve the contents of a vial of *dipyridamole for peak identification CRS* (containing impurities A, B, C, D, E and F) in 1 mL of *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of *potassium dihydrogen phosphate R* in 900 mL of *water R*, adjust to pH 7.0 with *0.5 M sodium hydroxide* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	40	60
5 - 19	40 → 5	60 → 95

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
19 - 24	5 → 40	95 → 60
24 - 29	40	60

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 295 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with *dipyridamole for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention With reference to dipyridamole (retention time = about 8 min): impurity B = about 0.2; impurity F = about 0.3; impurity D = about 0.9; impurity E = about 1.3; impurity C = about 1.6; impurity A = about 2.2.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity D and dipyridamole;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 1.7;

— *impurities A, B, C*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities D, E*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

To 0.250 g add 10 mL of *water R* and shake vigorously. Filter, rinse the filter with 5 mL of *water R* and dilute to 15 mL with *water R*.

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 70 mL of *methanol R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 50.46 mg of $C_{24}H_{40}N_8O_4$.

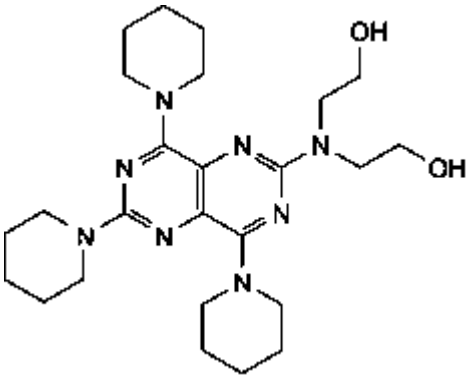
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E.*

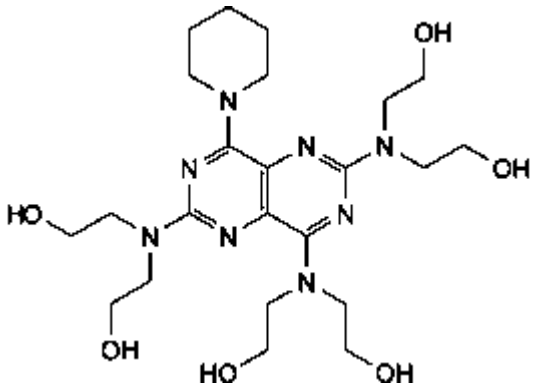
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F, G.*



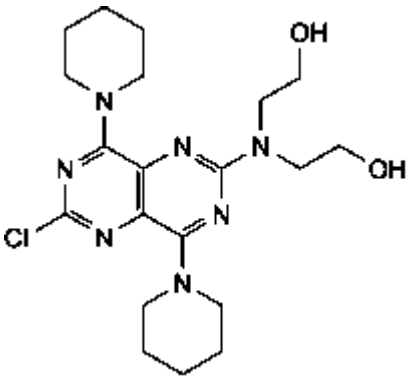
A. 2,2′-[[4,6,8-tri(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidin-2-yl]nitrilo]diethanol,

www.webofpharma.com

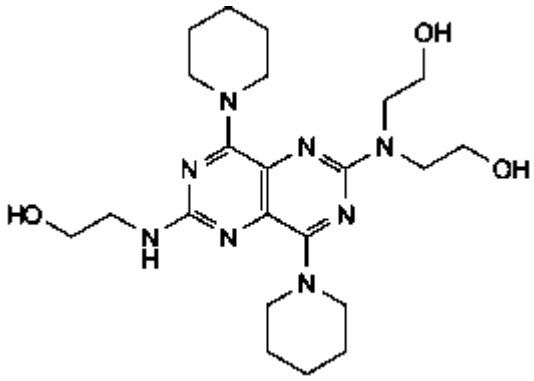
https://thuocngocanh.com/



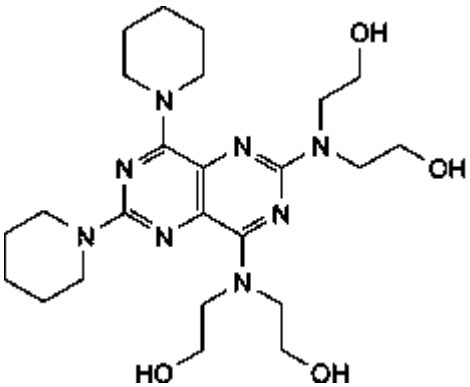
B. 2,2′,2″,2‴,2⁗,2⁗′[[8-(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine-2,4,6-triyl]trinitrilo]hexaethanol,



C. 2,2′-[[6-chloro-4,8-di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidin-2-yl]nitrilo]diethanol,



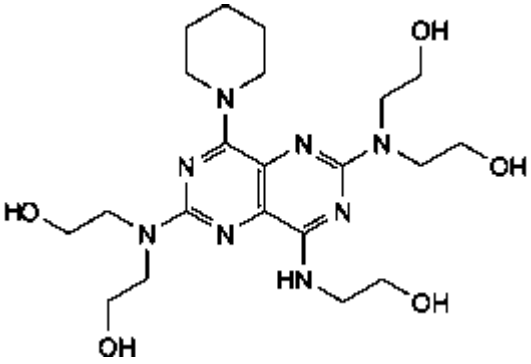
D. 2,2′-[[6-[(2-hydroxyethyl)amino]-4,8-di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidin-2-yl]nitrilo]diethanol,



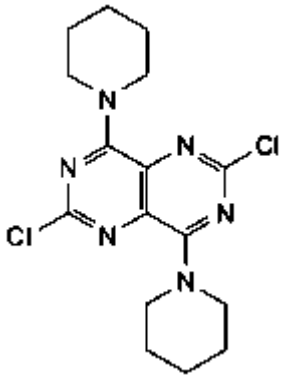
www.webofpharma.com

https://thuocngocanh.com/

E. 2,2′,2″,2‴-[[6,8-di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine-2,4-diyl]dinitrilo]tetraethanol,



F. 2,2′,2″,2‴-[[4-[(2-hydroxyethyl)amino]-8-(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine-2,6-diyl]dinitrilo]tetraethanol,



G. 2,6-dichloro-4,8-di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipyridamole Infusion

General Notices

Action and use

Adenosine reuptake inhibitor; inhibitor of platelet aggregation.

DEFINITION

Dipyridamole Infusion is a sterile solution containing Dipyridamole. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of dipyridamole, $C_{24}H_{40}N_8O_4$

93.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a volume of the infusion with a mixture of 1 volume of 0.1M *hydrochloric acid*, 4 volumes of *water* and 5 volumes of *methanol* to produce a solution containing 0.05% w/v of Dipyridamole and further dilute 1 volume of the resulting solution to 10 volumes with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 450 nm exhibits three maxima, at 231, 284 and 405 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak due to dipyridamole in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.5 to 3.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in amber glassware and protected from light.

(1) Dilute the infusion with *methanol (60%)* to produce a solution containing 0.01% w/v of Dipyridamole.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (60%)*.

(3) Dilute 1 volume of solution (2) to 5 volumes with *methanol (60%)*.

(4) Dissolve the contents of a vial of *dipyridamole for peak identification EPCRS* in 1 mL of *methanol (60%)*.

(5) 0.01% w/v of *dipyridamole impurity standard BPCRS* in *methanol (60%)*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 295 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 1.0 g of *potassium dihydrogen orthophosphate* in 900 mL of *water*, adjust to pH 7.0 with *0.5M sodium hydroxide* and dilute to 1000 mL with *water*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	40	60	isocratic
5-19	40→5	60→95	linear gradient
19-24	5→40	95→60	linear gradient
24-29	40	60	isocratic

SYSTEM SUITABILITY

The test is not valid unless;

the chromatogram obtained with solution (4) closely resembles the chromatogram supplied with *dipyridamole for peak identification EPCRS*;

the chromatogram obtained with solution (5) closely resembles the chromatogram supplied with *dipyridamole impurity standard BPCRS;*

in the chromatogram obtained with solution (4) the *resolution* between impurity D and dipyridamole is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity B using the chromatogram obtained with solution (4) and the chromatogram supplied with dipyridamole for peak identification EPCRS and multiply the area of this peak by a correction factor of 1.7;

the area of any peak corresponding to impurity 1 is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity A, B, or C is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak with an area less than 0.5 times that of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in amber glassware and protected from light.

(1) Dilute the infusion with *methanol (60%)* to produce a solution containing 0.005% w/v of Dipyridamole.
(2) 0.005% w/v of *dipyridamole BPCRS* in *methanol (60%)*.
(3) Dissolve the contents of a vial of *dipyridamole for peak identification EPCRS* in 1 mL of *methanol (60%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Related substances test may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *dipyridamole for peak identification EPCRS*;

the *resolution* between impurity D and dipyridamole is at least 2.0.

Calculate the content of $C_{24}H_{40}N_8O_4$ in the infusion using the declared content of $C_{24}H_{40}N_8O_4$ in *dipyridamole BPCRS*.

STORAGE

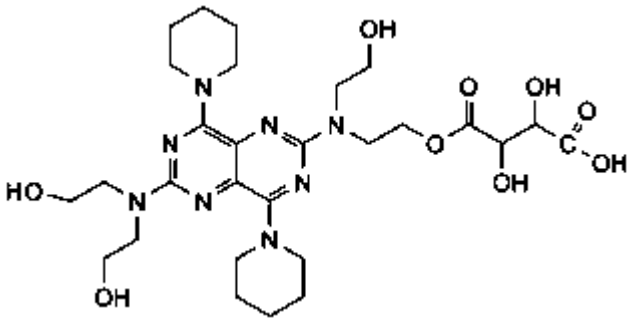
Dipyridamole Infusion should be protected from light.

IMPURITIES

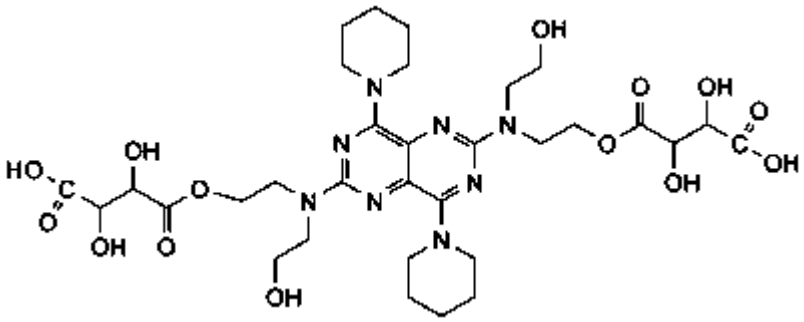
The impurities limited by the requirements of this monograph include those listed under Dipyridamole and the following:

www.webofpharma.com

https://thuocngocanh.com/



1. Dipyridamole tartaric acid monoester;



2. Dipyridamole ditartaric acid ester.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipyridamole Oral Suspension

General Notices

Action and use

Adenosine reuptake inhibitor; inhibitor of platelet aggregation.

DEFINITION

Dipyridamole Oral Suspension is a suspension of Dipyridamole in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of dipyridamole, $C_{24}H_{40}N_8O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To 10 mL of solution (1) prepared in the Assay add 1 mL of 1M *hydrochloric acid* and sufficient *methanol* to produce 100 mL. The *light absorption*, Appendix II B, of the solution in the range 220 to 450 nm, exhibits three maxima at 230, 285 and 405 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the peak due to dipyridamole in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 5.3 to 6.4, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in amber glassware and protected from light.

(1) To a volume of the oral suspension containing 50 mg of Dipyridamole add 1.0 g of *sodium chloride* and 20 mL of *water*, shake, add 90 mL of *methanol*, shake vigorously, cool and add sufficient *methanol* to produce 100 mL. Filter through a 0.45-µm nylon filter and dilute 10 mL of the filtrate to 20 mL with *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (50%)* and further dilute 1 volume of the resulting solution to 5 volumes with *methanol (50%)*.

(3) Dissolve the contents of a vial of *dipyridamole for peak identification EPCRS* in 1 mL of *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thatuocngocanh.com/

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 295 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 1.0 g of *potassium dihydrogen phosphate* in 900 mL of *water*, adjust to pH 7.0 with 0.5M *sodium hydroxide* and dilute to 1000 mL with *water*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	40	60	isocratic
5-19	40→5	60→95	linear gradient
19-24	5→40	95→60	linear gradient
24-29	40	60	isocratic

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *dipyridamole for peak identification EPCRS*;

the *resolution* between impurity D and dipyridamole is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

multiply the area of any peak corresponding to impurity B by a correction factor of 1.7;

the area of any peaks corresponding to impurity A, impurity B or impurity C is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peaks corresponding to impurity D or impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

www.webofpharma.com

https://thietbiuocngocanh.com/

the sum of the areas of any such peaks is not greater than 5 times the area of the peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than 0.5 times that of the peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in amber glassware and protected from light.

(1) To a weighed quantity of the oral suspension containing 50 mg of Dipyridamole add 1.0 g of *sodium chloride* and 20 mL of *water*, shake, add 90 mL of *methanol*, shake vigorously, cool and add sufficient *methanol* to produce 100 mL. Filter through a 0.45-µm nylon filter and dilute 10 mL of the filtrate to 100 mL with *methanol (50%)*.

(2) 0.005% w/v of *dipyridamole BPCRS* in *methanol (50%)*.

(3) Dissolve the contents of a vial of *dipyridamole for peak identification EPCRS* in 1 mL of *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Related substances test may be carried out.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *dipyridamole for peak identification EPCRS*;

the *resolution* between impurity D and dipyridamole is at least 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{24}H_{40}N_8O_4$, weight in volume, using the declared content of $C_{24}H_{40}N_8O_4$ in *dipyridamole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Dipyridamole.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipyridamole Prolonged-release Capsules

General Notices

Prolonged-release Dipyridamole Capsules

Dipyridamole Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Adenosine reuptake inhibitor; inhibitor of platelet aggregation.

DEFINITION

Dipyridamole Prolonged-release Capsules contain Dipyridamole. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Dipyridamole. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of dipyridamole, $C_{24}H_{40}N_8O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered capsule contents containing 50 mg of Dipyridamole with 20 mL of *dichloromethane*, filter and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dipyridamole *(RS 108)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in amber glassware and protected from light.

(1) Shake, with the aid of ultrasound for 5 minutes, a quantity of the powdered capsule contents containing 0.2 g of Dipyridamole with 10 mL of *methanol (60%)*, dilute to 100 mL with *methanol (60%)*, filter through a 0.45-µm filter and use the clear solution.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (60%)*.

(3) 0.05% w/v of *dipyridamole impurity standard BPCRS* in *methanol (60%)*.

(4) Dissolve the contents of a vial of *dipyridamole for peak identification EPCRS* in 1 mL of *methanol (60%)*.

(5) Dilute 1 volume of solution (2) to 20 volumes with *methanol (60%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 1.0 g of *potassium dihydrogen orthophosphate* in 900 mL of *water*, adjust to pH 7.0 with 0.5M *sodium hydroxide* and dilute to 1000 mL with *water*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	40	60	isocratic
5-19	40→5	60→95	linear gradient
19-24	5→40	95→60	linear gradient
24-29	40	60	isocratic

SYSTEM SUITABILITY

The test is not valid unless:

the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *dipyridamole impurity standard BPCRS;*

the chromatogram obtained with solution (4) closely resembles the chromatogram supplied with *dipyridamole for peak identification EPCRS*;

in the chromatogram obtained with solution (4) the *resolution* between impurity D and dipyridamole is at least 2.0.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity B using the chromatogram obtained with solution (4) and the chromatogram supplied with dipyridamole for peak identification EPCRS and multiply the area of this peak by a correction factor of 1.7;

the area of any peak corresponding to impurity 1 is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%);

the area of any peak corresponding to impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity A, B, C, D or E is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of all secondary peaks is not greater than 5.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5.5%).

Disregard any peak with an area less than the area of principal peak in the chromatogram obtained with solution (5) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in amber glassware and protected from light.

(1) Shake with the aid of ultrasound for 5 minutes, a quantity of the mixed contents of 20 capsules containing 50 mg of Dipyridamole with 10 mL of *methanol (60%)*, dilute to 100 mL with *methanol (60%)* and filter through a 0.45-µm filter. Dilute 10 mL of the filtrate to 100 mL with the mobile phase.

(2) 0.005% w/v of *dipyridamole BPCRS* in *methanol (60%)*.

(3) Dissolve the contents of a vial of *dipyridamole for peak identification EPCRS* in 1 mL of *methanol (60%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions procedure described under Related substances test may be used.

SYSTEM SUITABILITY

The Assay is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *dipyridamole for peak identification EPCRS*;

the *resolution* between the peaks due to impurity D and dipyridamole is at least 2.0.

DETERMINATION OF CONTENT

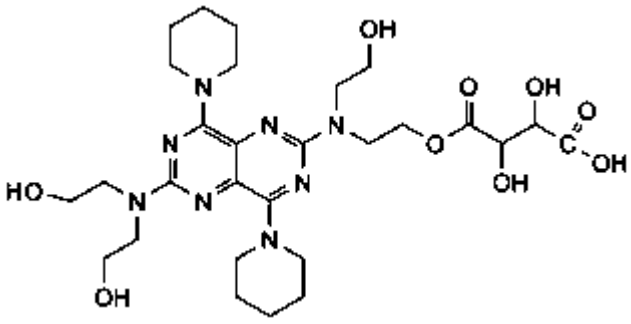
Calculate the content of $C_{24}H_{40}N_8O_4$ in the capsules using the declared content of $C_{24}H_{40}N_8O_4$ in *dipyridamole BPCRS*.

IMPURITIES

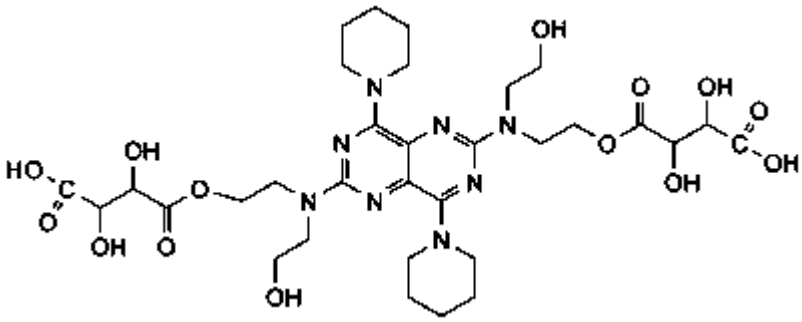
www.webofpharma.com

https://thuocngocanh.com/

The impurities limited by the requirements of this monograph include those listed under Dipyridamole and the following:



1. Dipyridamole tartaric acid monoester,



2. Dipyridamole ditartaric acid ester.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipyridamole Tablets

General Notices

Action and use

Adenosine reuptake inhibitor; inhibitor of platelet aggregation.

DEFINITION

Dipyridamole Tablets contain Dipyridamole. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dipyridamole, $C_{24}H_{40}N_8O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 50 mg of Dipyridamole with 20 mL of *dichloromethane*, filter and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dipyridamole *(RS 108)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in amber glassware and protected from light.

(1) Shake a quantity of the powdered tablets containing 50 mg of Dipyridamole with 100 mL of *methanol (60%)* for 15 minutes, filter (Whatman GF/C filter is suitable) and use the filtrate.

(2) Dilute 1 mL of solution (1) to 200 mL with *methanol (60%)*.

(3) Dissolve the contents of a vial of *dipyridamole for peak identification EPCRS* (dipyridamole and impurities A to F) in 1 mL of *methanol (60%)*.

(4) Dilute 1 mL of solution (2) to 10 mL with *methanol (60%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use a column temperature of 45°.

www.webofpharma.com

https://thuvienthuocngocanh.com/

(e) Use a detection wavelength of 290 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 1.0 g of *potassium dihydrogen orthophosphate* in 900 mL of *water*, adjust to pH 7.0 with 0.5M *sodium hydroxide* and dilute to 1000 mL with *water*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	40	60	isocratic
5-19	40→5	60→95	linear gradient
19-24	5→40	95→60	linear gradient
24-29	40	60	isocratic

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *dipyridamole for peak identification EPCRS*;

the *resolution factor* between impurity D and dipyridamole is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity B and multiply the area of this peak by a correction factor of 1.7;

the area of any peak corresponding to impurity A, B, C, D or E is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in amber glassware and protected from light.

www.webofpharma.com

https://thuocngocanh.com/

(1) Shake a quantity of the powdered tablets containing 50 mg of Dipyridamole with 100 mL of *methanol (60%)* for 15 minutes and filter (Whatman GF/C is suitable). Dilute 1 mL of the filtrate to 10 mL with *methanol (60%)*.

(2) 0.005% w/v of *dipyridamole BPCRS* in *methanol (60%)*.

(3) Dissolve the contents of a vial of *dipyridamole for peak identification EPCRS* (dipyridamole and impurities A to F) in 1 mL of *methanol (60%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Related substances test may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the chromatogram supplied with *dipyridamole for peak identification EPCRS*;

the *resolution factor* between impurity D and dipyridamole is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{40}N_8O_4$ in the tablets using the declared content of $C_{24}H_{40}N_8O_4$ in *dipyridamole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Dipyridamole.

© Crown Copyright 2022

www.webofpharma.com

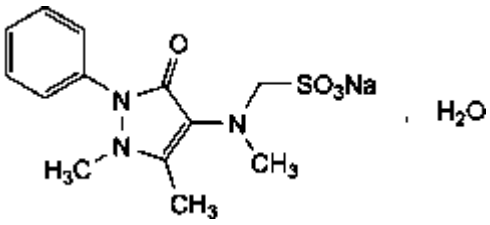
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dipyrone

General Notices

(Metamizole Sodium Monohydrate, Ph. Eur. monograph 1346)



$C_{13}H_{16}N_3NaO_4S,H_2O$ 351.4 *5907-38-0*

Action and use

Analgesic.

Ph Eur

DEFINITION

Sodium [(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(methyl)amino]methanesulfonate monohydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *metamizole sodium CRS*.

B. Dissolve 50 mg in 1 mL of *strong hydrogen peroxide solution R*. A blue colour is produced which fades rapidly and turns to intense red in a few minutes.

C. Place 0.10 g in a test tube, add some glass beads and dissolve the substance in 1.5 mL of *water R*. Add 1.5 mL of *dilute hydrochloric acid R* and place a filter paper wetted with a solution of 20 mg of *potassium iodate R* in 2 mL of *starch solution R* at the open end of the test tube. Heat gently, the evolving vapour of sulfur dioxide colours the filter paper blue. After heating gently for 1 min, take a glass rod with a drop of a 10 g/L solution of *chromotropic acid, sodium salt R* in *sulfuric acid R* and place in the opening of the tube. Within 10 min, a blue-violet colour develops in the drop of the reagent.

D. 0.5 mL of solution S (see Tests) gives reaction (a) of sodium (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 40 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and, immediately after preparation, not more intensely coloured than reference solution BY_6 (2.2.2, *Method I*).

Acidity or alkalinity

To 5 mL of solution S, add 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.1 mL of *0.02 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *metamizole impurity A CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase. Use 1.0 mL of this solution to dissolve the contents of a vial of *metamizole impurity E CRS*.

Reference solution (c) In order to prepare impurity C *in situ*, dissolve 40 mg of the substance to be examined in *methanol R*, dilute to 20 mL with the same solvent and boil under reflux for 10 min. Allow to cool to room temperature and dilute to 20 mL with *methanol R*.

Reference solution (d) Dilute 1.0 mL of reference solution (a) to 100.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (1.8 µm).

Mobile phase Mix 28 volumes of *methanol R* and 72 volumes of a buffer solution prepared as follows: mix 1000 volumes of a 6.0 g/L solution of *sodium dihydrogen phosphate R* and 1 volume of *triethylamine R*, then adjust to pH 7.0 with *strong sodium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 5 µL of the test solution and reference solutions (b), (c) and (d).

Run time 4.5 times the retention time of metamizole.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to metamizole (retention time = about 2 min): impurity A = about 0.7; impurity E = about 0.8; impurity C = about 2.5.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity E.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 1.5;

— *impurity C*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *impurity E*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.03 per cent).

Sulfates (*2.4.13*)

Maximum 0.1 per cent.

Dissolve 0.150 g in *distilled water R* and dilute to 15 mL with the same solvent.

Loss on drying (*2.2.32*)

www.webofpharma.com

https://thuocngocanh.com/

4.9 per cent to 5.3 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.200 g in 10 mL of *0.01 M hydrochloric acid* previously cooled in iced water and titrate immediately, dropwise, with *0.05 M iodine*. Before each addition of *0.05 M iodine* dissolve the precipitate by swirling. At the end of the titration, add 2 mL of *starch solution R* and titrate until the blue colour of the solution persists for at least 2 min. The temperature of the solution during the titration must not exceed 10 °C.

1 mL of *0.05 M iodine* is equivalent to 16.67 mg of $C_{13}H_{16}N_3NaO_4S$.

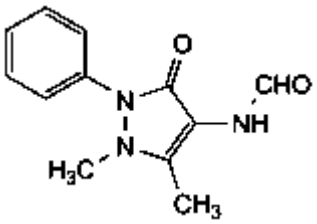
STORAGE

Protected from light.

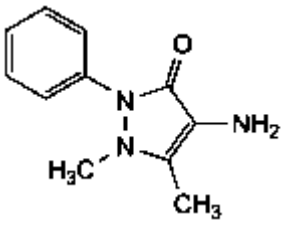
IMPURITIES

Specified impurities C, E.

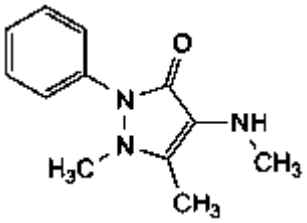
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D.



A. 4-(formylamino)-1,5-dimethyl-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-one,



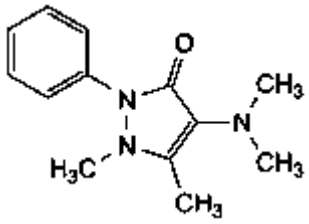
B. 4-amino-1,5-dimethyl-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-one,



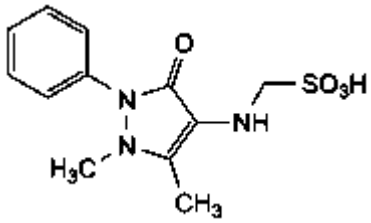
www.webofpharma.com

https://thuocngocanh.com/

C. 1,5-dimethyl-4-(methylamino)-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-one,



D. 1,5-dimethyl-4-(dimethylamino)-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-one,



E. [(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino]methanesulfonic acid (4-*N*-desmethylmetamizole).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

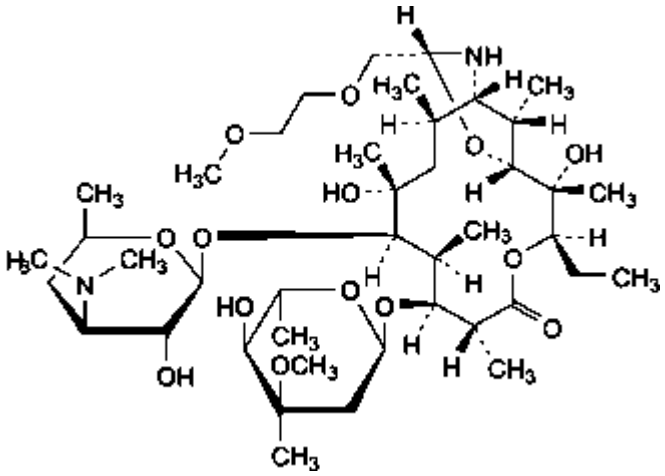
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dirithromycin

General Notices

(Ph. Eur. monograph 1313)



$C_{42}H_{78}N_2O_{14}$ 835 *62013-04-1*

Action and use

Macrolide antibacterial.

Ph Eur

DEFINITION

(1*R*,2*S*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*,13*S*,15*R*,17*S*)-9-[[3-(Dimethylamino)-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-3-ethyl-2,10-dihydroxy-15-[(2-methoxyethoxy)methyl]-2,6,8,10,12,17-hexamethyl-7-[(3-*C*-methyl-3-*O*-methyl-2,6dideoxy-α-L-*ribo*-hexopyranosyl)oxy]-4,16-dioxa-14azabicyclo[11.3.1]heptadecan-5-one (or (9*S*)-9,11-[imino[(1*R*)-2-(2-methoxyethoxy)ethylidene]oxy]-9-deoxo-11-deoxyerythromycin).

Semi-synthetic product derived from a fermentation product.

Content

96.0 per cent to 102.0 per cent for the sum of the percentage contents of $C_{42}H_{78}N_2O_{14}$ and dirithromycin 15*S*-epimer (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuvienthuocngocanh.com/

White or almost white powder.

Solubility

Very slightly soluble in water, very soluble in methanol and in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison dirithromycin CRS.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (a) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture methanol R, acetonitrile R1 (30:70 *V/V*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dissolve 0.10 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 20.0 mg of dirithromycin CRS in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 20 mg of dirithromycin CRS in the mobile phase and dilute to 10 mL with the mobile phase. Allow to stand for 24 h before use.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 9 volumes of water R, 19 volumes of methanol R, 28 volumes of a solution containing 1.9 g/L of potassium dihydrogen phosphate R and 9.1 g/L of dipotassium hydrogen phosphate R adjusted to pH 7.5 if necessary with a 100 g/L solution of potassium hydroxide R, and 44 volumes of acetonitrile R1.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 10 µL of test solution (b) and reference solutions (b) and (c).

Run time 3 times the retention time of dirithromycin.

Relative retention With reference to dirithromycin: impurity A = about 0.7; 15*S*-epimer = about 1.1.

System suitability Reference solution (c):

— *resolution*: minimum 2.0 between the peaks due to dirithromycin and its 15*S*-epimer; if necessary, adjust the concentration of the organic modifiers in the mobile phase.

Limits:

— *impurity A*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *disregard limit*: disregard the peak due to the 15*S*-epimer.

Dirithromycin 15*S*-epimer

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (b).

System suitability Reference solution (b):

— *repeatability*: maximum relative standard deviation of 5.0 per cent after 6 injections.

Limit:

— *15S-epimer*: maximum 1.5 per cent.

Acetonitrile (2.4.24, System A)

Maximum 0.1 per cent.

Prepare the solutions using *dimethylformamide R* instead of *water R*.

Sample solution Dissolve 0.200 g of the substance to be examined in *dimethylformamide R* and dilute to 20.0 mL with the same solvent.

Static head-space injection conditions that may be used:

— *equilibration temperature*: 120 °C;

www.webofpharma.com

https://thuocngocanh.com/

— *equilibration time*: 60 min;

— *transfer-line temperature*: 125 °C.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (a) and reference solution (a).

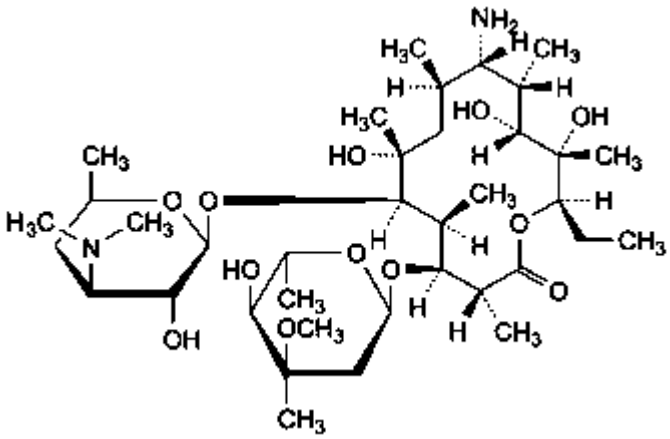
System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

IMPURITIES

Specified impurities *A.*

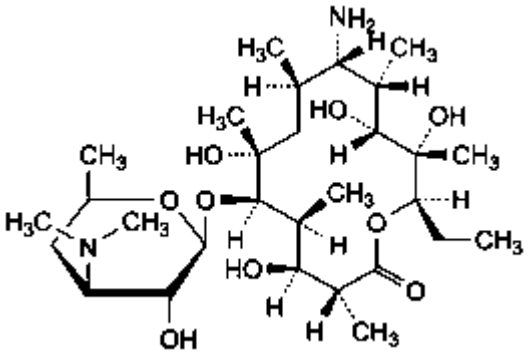
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E.*



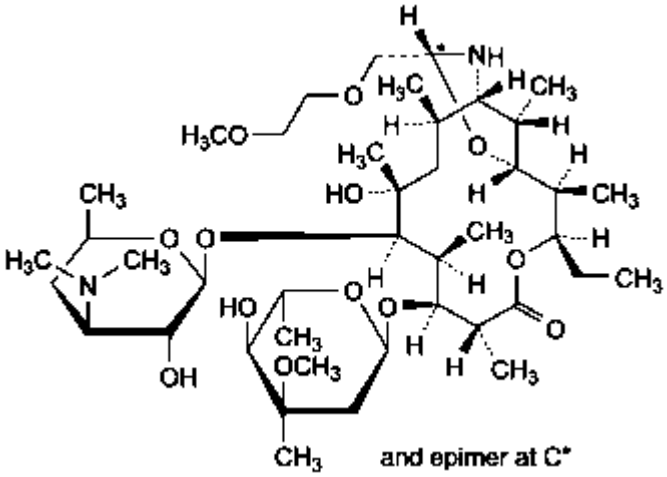
A. (9*S*)-9-amino-9-deoxoerythromycin,

www.webofpharma.com

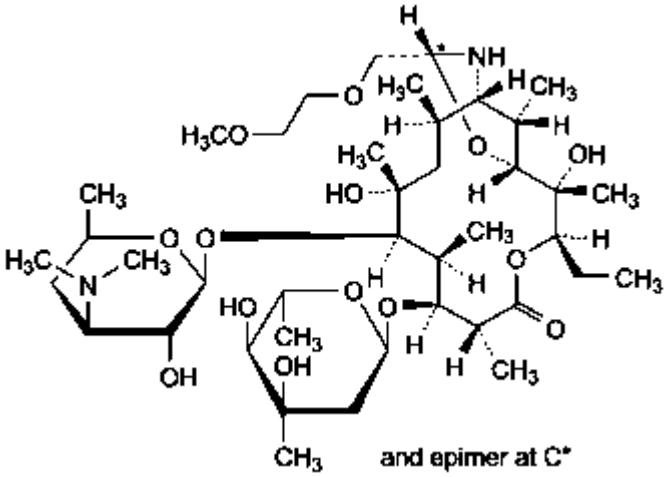
https://thuocngocanh.com/



B. (9*S*)-9-amino-3-de(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)-9-deoxoerythromycin,



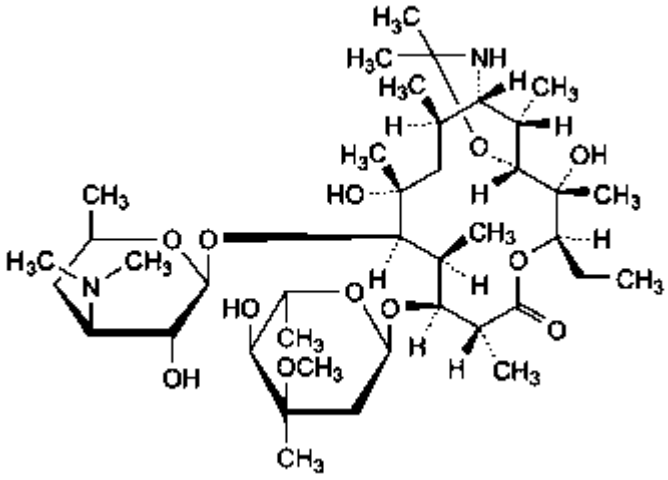
C. (9*S*)-9,11-[imino[(1*RS*)-2-(2-methoxyethoxy)ethylidene]oxy]-9-deoxo-11,12-dideoxyerythromycin (dirithromycin B),



D. (9*S*)-9,11-[imino[(1*RS*)-2-(2-methoxyethoxy)ethylidene]oxy]-3′-*O*-demethyl-9-deoxo-11-deoxyerythromycin (dirithromycin C),

www.webofpharma.com

https://thuvienthuocngocanh.com/



E. 9,11-[imino(1-methylethylidene)oxy]-9-deoxo-11-deoxyerythromycin.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

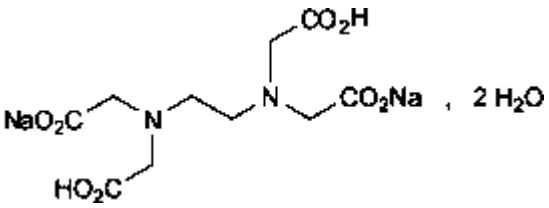
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disodium Edetate

General Notices

(Ph. Eur. monograph 0232)



$C_{10}H_{14}N_2Na_2O_8,2H_2O$ 372.2

Action and use

Chelating agent.

Preparations

Disodium Edetate Eye Drops

Trisodium Edetate Infusion

Ph Eur

DEFINITION

Disodium dihydrogen (ethylenedinitrilo)tetraacetate dihydrate.

Content

98.5 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, B, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *disodium edetate CRS*.

B. Dissolve 2 g in 25 mL of *water R*, add 6 mL of *lead nitrate solution R*, shake and add 3 mL of *potassium iodide solution R*. No yellow precipitate is formed. Make alkaline to *red litmus paper R* by the addition of *dilute ammonia R2*. Add 3 mL of *ammonium oxalate solution R*. No precipitate is formed.

C. Dissolve 0.5 g in 10 mL of *water R* and add 0.5 mL of *calcium chloride solution R*. Make alkaline to *red litmus paper R* by the addition of *dilute ammonia R2* and add 3 mL of *ammonium oxalate solution R*. No precipitate is formed.

D. It gives the reactions of sodium (2.3.1).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (*2.2.2, Method II*).

pH (2.2.3)

4.0 to 5.5 for solution S.

Impurity A

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture Dissolve 10.0 g of *ferric sulfate pentahydrate R* in 20 mL of *0.5 M sulfuric acid* and add 780 mL of *water R*. Adjust to pH 2.0 with *1 M sodium hydroxide* and dilute to 1000 mL with *water R*.

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution Dissolve 40.0 mg of *nitrilotriacetic acid R* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. To 1.0 mL of the solution add 0.1 mL of the test solution and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: *graphitised carbon for chromatography R* (5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Dissolve 50.0 mg of *ferric sulfate pentahydrate R* in 50 mL of *0.5 M sulfuric acid* and add 750 mL of *water for chromatography R*. Adjust to pH 1.5 with *0.5 M sulfuric acid* or *1 M sodium hydroxide*, add 20 mL of *ethylene glycol R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 273 nm.

Injection 20 µL; filter the solutions and inject immediately.

Run time 4 times the retention time of the iron complex of impurity A.

Retention times Iron complex of impurity A = about 5 min; iron complex of edetic acid = about 10 min.

System suitability Reference solution:

— *resolution*: minimum 7.0 between the peaks due to the iron complex of impurity A and the iron complex of edetic acid,

— *signal-to-noise ratio*: minimum 50 for the peak due to impurity A.

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Iron (*2.4.9*)

Maximum 80 ppm.

Dilute 2.5 mL of solution S to 10 mL with *water R*. Add 0.25 g of *calcium chloride R* to the test solution and the standard before the addition of the *thioglycollic acid R*.

ASSAY

Dissolve 0.300 g in *water R* and dilute to 300 mL with the same solvent. Add 2 g of *hexamethylenetetramine R* and 2 mL of *dilute hydrochloric acid R*. Titrate with *0.1 M lead nitrate*, using about 50 mg of *xylenol orange triturate R* as indicator.

1 mL of *0.1 M lead nitrate* is equivalent to 37.22 mg of $C_{10}H_{14}N_2Na_2O_8,2H_2O$.

STORAGE

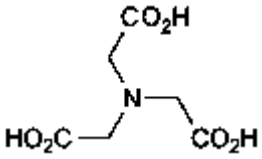
Protected from light.

IMPURITIES

Specified impurities *A*.

www.webofpharma.com

https://thuocngocanh.com/



A. nitrilotriacetic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disodium Edetate Eye Drops

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Chelating agent.

DEFINITION

Disodium Edetate Eye Drops are a sterile solution of Disodium Edetate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements. Where appropriate, the eye drops also comply with the requirements stated under Unlicensed Medicines.

Content of disodium edetate, $C_{10}H_{14}N_2Na_2O_8,2H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Add 6 mL of *lead nitrate solution* to 25 mL of the eye drops, shake and add 3 mL of *potassium iodide solution*; no yellow precipitate is produced. Make alkaline to *red litmus paper* with *dilute ammonia R2* and add 3 mL of *ammonium oxalate solution*; no precipitate is produced.

B. Add 0.5 mL of *calcium chloride solution* to 10 mL of the eye drops, make alkaline to *red litmus paper* with *dilute ammonia R2* and add 3 mL of *ammonium oxalate solution*; no precipitate is produced.

C. Yield the reactions characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

pH, 6.0 to 7.5, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the eye drops containing 20 mg of Disodium Edetate with sufficient *water* to produce 100 mL.

(2) 0.02% w/v of *disodium edetate BPCRS* in *water*.

Before injection, mix solutions (1) and (2) with an equal volume of a 0.04% w/v solution of *copper(II) nitrate*.

www.webofpharma.com

https://thietbiuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak or Bondclone C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Add 6 volumes of *tetrabutylammonium hydroxide solution* to 195 volumes of *water*; adjust the pH to 6.5 with *orthophosphoric acid*, add 200 volumes of *acetonitrile* and sufficient *water* to produce 1000 volumes.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{14}N_2Na_2O_8,2H_2O$ in the eye drops using the declared content of $C_{10}H_{14}N_2Na_2O_8,2H_2O$ in *disodium edetate BPCRS*.

STORAGE

Disodium Edetate Eye Drops should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disodium Hydrogen Phosphate

General Notices

Anhydrous Disodium Hydrogen Phosphate

(Disodium Phosphate, Ph. Eur. monograph 1509)

Na_2HPO_4 142.0 *7558-79-4*

Action and use

Excipient.

Preparation

Phosphates Enema

Ph Eur

DEFINITION

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly alkaline (*2.2.4*).

B. Loss on drying (see Tests).

C. Solution S gives reaction (b) of phosphates (*2.3.1*).

D. Solution S gives reaction (a) of sodium (*2.3.1*).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 5.0 g in *distilled water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Reducing substances

To 10 mL of solution S add 5 mL of *dilute sulfuric acid R* and 0.25 mL of a 3.2 g/L solution of *potassium permanganate R* and heat on a water-bath for 5 min. The colour of the permanganate is not completely discharged.

Monosodium phosphate

Maximum 2.5 per cent.

From the volumes of *1 M sodium hydroxide* (n_1 mL, n_2 mL and n_3 mL) used in the assay, calculate the following ratio:

$$\frac{n_2 - n_3}{n_3 - n_1}$$

This ratio is not greater than 0.025.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 15 mL with *dilute nitric acid R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

To 6 mL of solution S add 2 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 20 ppm, determined on solution S.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

ASSAY

Dissolve 1.600 g (*m*) in 25.0 mL of *carbon dioxide-free water R* and add 25.0 mL of *1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*) using *1 M sodium hydroxide*. Read the volume added at the 1st inflexion point (n_1 mL). Continue the titration to the 2nd inflexion point (total volume of *1 M sodium hydroxide* required, n_2 mL). Carry out a blank titration (n_3 mL).

Calculate the percentage content of Na_2HPO_4 from the following expression:

www.webofpharma.com

https://thuocngocanh.com/

$$\frac{1420\left(n_3 - n_1\right)}{m\left(100 - d\right)}$$

d = percentage loss on drying.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disodium Hydrogen Phosphate Dihydrate

General Notices

Sodium Phosphate Dihydrate

(Disodium Phosphate Dihydrate, Ph. Eur. monograph 0602)

$Na_2HPO_4,2H_2O$ 178.0 *10028-24-7*

Action and use

Excipient.

Preparations

Phosphates Enema

Phosphate Oral Solution

Ph Eur

DEFINITION

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder or colourless crystals.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly alkaline (*2.2.4*).

B. Loss on drying (see Tests).

C. Solution S gives reaction (b) of phosphates (*2.3.1*).

D. Solution S gives reaction (a) of sodium (*2.3.1*).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 5.0 g in *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Reducing substances

To 5 mL of solution S add 5 mL of *dilute sulfuric acid R* and 0.25 mL of a 3.2 g/L solution of *potassium permanganate R* and heat on a water-bath for 5 min. The colour of the permanganate is not completely discharged.

Monosodium phosphate

Maximum 2.5 per cent.

From the volumes of *1 M sodium hydroxide* (n_1 mL, n_2 mL and n_3 mL) used in the assay, calculate the following ratio:

$$\frac{n_2 - n_3}{n_3 - n_1}$$

This ratio is not greater than 0.025.

Chlorides (*2.4.4*)

Maximum 400 ppm.

To 2.5 mL of solution S add 10 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 0.1 per cent.

To 3 mL of solution S add 2 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 40 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

19.5 per cent to 21.0 per cent, determined on 1.000 g by drying in an oven at 130 °C.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 2.000 g (*m*) in 50 mL of *water R* and add 25.0 mL of *1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*) using *1 M sodium hydroxide*. Read the volume added at the 1st inflexion point (n_1 mL). Continue the titration to the 2nd inflexion point (total volume of *1 M sodium hydroxide* required, n_2 mL). Carry out a blank titration (n_3 mL).

Calculate the percentage content of Na_2HPO_4 from the following expression:

$$\frac{1420\left(n_3 - n_1\right)}{m\left(100 - d\right)}$$

d = percentage loss on drying.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disodium Hydrogen Phosphate Dodecahydrate

General Notices

Disodium Hydrogen Phosphate

Sodium Phosphate

(Disodium Phosphate Dodecahydrate, Ph. Eur. monograph 0118)

$Na_2HPO_4,12H_2O$ 358.1 *10039-32-4*

Preparation

Phosphates Enema

Ph Eur

DEFINITION

Content

98.5 per cent to 102.5 per cent.

CHARACTERS

Appearance

Colourless, transparent crystals, very efflorescent.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Solution S (see Tests) is slightly alkaline (*2.2.4*).

B. Loss on drying (see Tests).

C. Solution S gives reaction (b) of phosphates (*2.3.1*).

D. Solution S gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 5.0 g in *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Reducing substances

To 5 mL of solution S add 5 mL of *dilute sulfuric acid R* and 0.25 mL of a 3.2 g/L solution of *potassium permanganate R* and heat on a water-bath for 5 min. The colour of the permanganate is not completely discharged.

Monosodium phosphate

Maximum 2.5 per cent.

From the volumes of *1 M sodium hydroxide* (n_1 mL, n_2 mL and n_3 mL) used in the assay, calculate the following ratio:

$$\frac{n_2 - n_3}{n_3 - n_1}$$

This ratio is not greater than 0.025.

Chlorides (*2.4.4*)

Maximum 200 ppm.

To 2.5 mL of solution S add 10 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 500 ppm.

To 3 mL of solution S add 2 mL of *dilute hydrochloric acid R* and dilute to 15 mL with *distilled water R*.

Iron (*2.4.9*)

Maximum 20 ppm.

Dilute 5 mL of solution S to 10 mL with *water R*.

Loss on drying (*2.2.32*)

57.0 per cent to 61.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 4 h.

ASSAY

Dissolve 4.000 g (*m*) in 25 mL of *water R* and add 25.0 mL of *1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*) using *1 M sodium hydroxide*. Read the volume added at the 1st inflexion point (n_1 mL). Continue the titration to the 2nd inflexion point (total volume of *1 M sodium hydroxide* required, n_2 mL). Carry out a blank titration (n_3 mL).

www.webofpharma.com

https://thuocngocanh.com/

Calculate the percentage content of $Na_2HPO_4,12H_2O$ using the following expression:

$$\frac{3581\left(n_3-n_1\right)}{m\times 100}$$

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

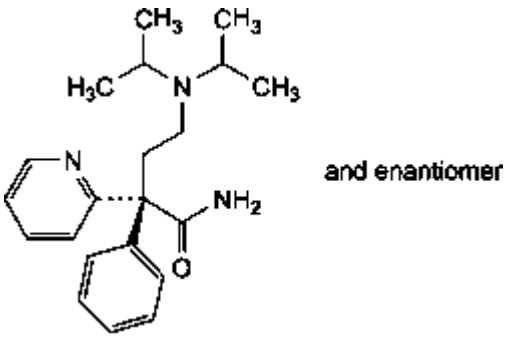
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disopyramide

General Notices

(Ph. Eur. monograph 1006)



$C_{21}H_{29}N_3O$ 339.5 *3737-09-5*

Action and use

Class I antiarrhythmic.

Preparation

Disopyramide Capsules

Ph Eur

DEFINITION

(2*RS*)-4-[Di(propan-2-yl)amino]-2-phenyl-2-(pyridin-2-yl)butanamide

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, freely soluble in methylene chloride, soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Place 50 µL of a 50 g/L solution in *methylene chloride R* on a disc of *potassium bromide R*. Dry the disc at 60 °C for 1 h.

Comparison *disopyramide CRS*.

B. Examine the chromatograms obtained in the test for related substances.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *dilute potassium iodobismuthate solution R*; examine in daylight.

Results B The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.20 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 20 mg of *disopyramide CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 0.5 mL of test solution (b) to 20 mL with *methanol R*.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *concentrated ammonia R*, *acetone R*, *cyclohexane R* (1:30:30 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of warm air.

Detection Examine in ultraviolet light at 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Retardation factor Disopyramide = about 0.4.

Limit:

— *any impurity*: any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.25 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

maximum 0.2 per cent, determined on 1.0 g.

ASSAY

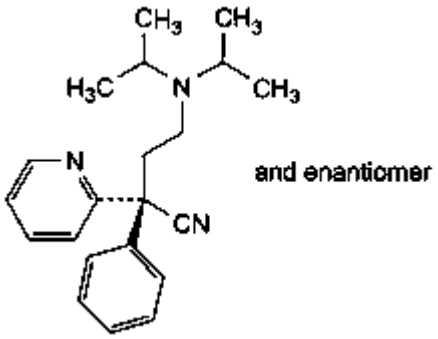
Dissolve 0.130 g in 30 mL of *anhydrous acetic acid R*. Add 0.2 mL of *naphtholbenzein solution R*. Titrate with *0.1 M perchloric acid* until the colour changes from yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 16.97 mg of $C_{21}H_{29}N_3O$.

STORAGE

Protected from light.

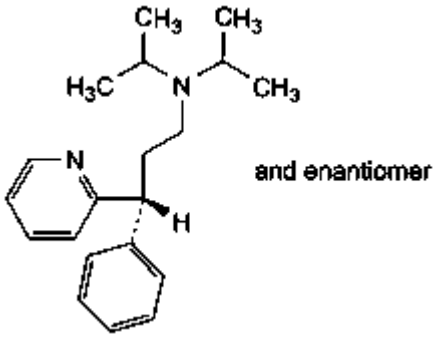
IMPURITIES



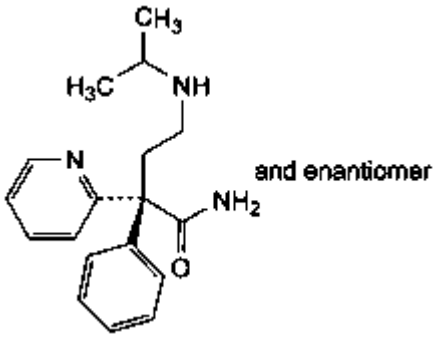
A. (2*RS*)-4-di(propan-2-yl)amino]-2-phenyl-2-(pyridin-2-yl)butanenitrile (di-isopyronitrile),

www.webofpharma.com

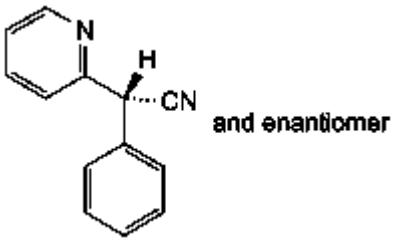
https://thuocngocanh.com/



B. (3*RS*)-3-phenyl-*N*,*N*-di(propan-2-yl)-3-(pyridin-2-yl)propan-1-amine,



C. (2*RS*)-2-phenyl-4-[(propan-2-yl)amino]-2-(pyridin-2-yl)butanamide,



D. (*RS*)-phenyl(pyridin-2-yl)acetonitrile (pyronitrile).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disopyramide Capsules

General Notices

Action and use

Class I antiarrhythmic.

DEFINITION

Disopyramide Capsules contain Disopyramide.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of disopyramide, $C_{21}H_{29}N_3O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing 0.2 g of Disopyramide with 50 mL of *chloroform* for 15 minutes, filter, evaporate the filtrate to dryness using a rotary evaporator and dissolve the residue in 2 mL of *chloroform*. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of disopyramide *(RS 110)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution obtained in the Assay exhibits a maximum only at 269 nm.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 0.20 g of Disopyramide with 20 mL of *methanol* for 30 minutes and filter.

(2) Dilute 1 volume of solution (1) to 400 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel GF_{254} plate*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

1 volume of 18M *ammonia*, 30 volumes of *acetone* and 30 volumes of *cyclohexane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.25%).

ASSAY

To a quantity of the mixed contents of 20 capsules containing 40 mg of Disopyramide, add 40 mL of 0.05M *methanolic sulfuric acid*, shake for 15 minutes, dilute to 100 mL with the same solvent and filter. Dilute 5 mL of the filtrate to 100 mL with 0.05M *methanolic sulfuric acid* and measure the *absorbance* of the resulting solution at the maximum at 269 nm, Appendix II B. Calculate the content of $C_{21}H_{29}N_3O$ taking 198.5 as the value of A(1%, 1 cm) at the maximum at 269 nm.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

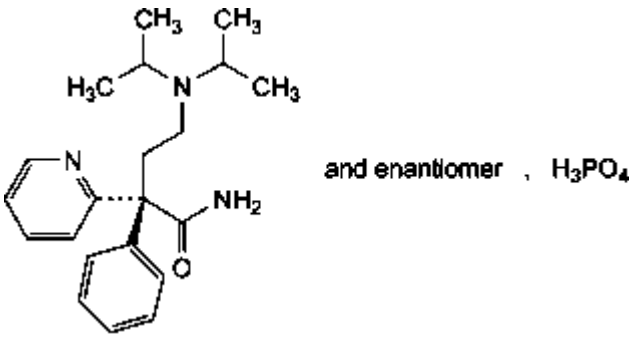
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Disopyramide Phosphate

General Notices

(Ph. Eur. monograph 1005)



$C_{21}H_{32}N_3O_5P$ 437.5 *22059-60-5*

Action and use

Antiarrhythmic.

Preparation

Disopyramide Phosphate Capsules

Ph Eur

DEFINITION

Disopyramide phosphate contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of (2*RS*)-4-[bis(1-methylethyl)amino]-2-phenyl-2-(pyridin-2-yl)butanamide dihydrogen phosphate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white powder, soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Dissolve 50.0 mg in a 5 g/L solution of *sulfuric acid R* in *methanol R* and dilute to 100.0 mL with the same solution. Dilute 5.0 mL of this solution to 50.0 mL with a 5 g/L solution of *sulfuric acid R* in *methanol R*. Examined between 240 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 269 nm and a shoulder at 263 nm. The specific absorbance at the maximum is 147 to 163.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *disopyramide phosphate CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for related substances in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a). Spray with *dilute potassium iodobismuthate solution R*. Examine in daylight. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Solution S (see Tests) gives reaction (a) of phosphates (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 4.0 to 5.0.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel GF_{254} R* as the coating substance.

Test solution (a) Dissolve 0.25 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 25 mg of *disopyramide phosphate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1 mL of test solution (b) to 20 mL with *methanol R*.

Apply to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *concentrated ammonia R*, 30 volumes of *acetone R* and 30 volumes of *cyclohexane R*. Dry the plate in a current of warm air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

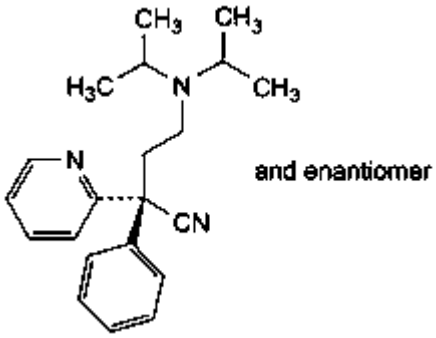
Dissolve 0.180 g in 30 mL of *anhydrous acetic acid R*. Add 0.2 mL of *naphtholbenzein solution R*. Titrate with *0.1 M perchloric acid* until the colour changes from yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 21.88 mg of $C_{21}H_{32}N_3O_5P$.

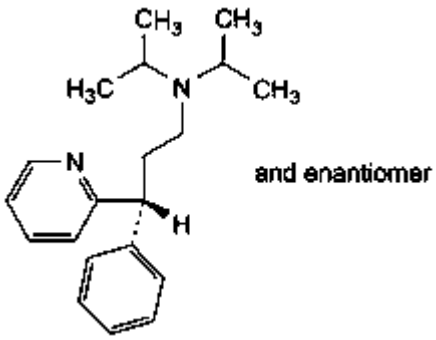
STORAGE

Store protected from light.

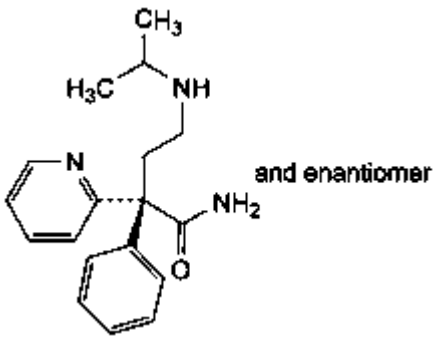
IMPURITIES



A. (2*RS*)-4-[bis(1-methylethyl)amino]-2-phenyl-2-(pyridin-2-yl)butanenitrile (di-isopyronitrile),



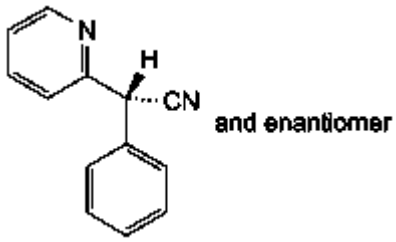
B. (3*RS*)-*N*,*N*-bis(1-methylethyl)-3-phenyl-3-(pyridin-2-yl)propan-1-amine,



C. (2*RS*)-4-[(1-methylethyl)amino]-2-phenyl-2-(pyridin-2-yl)butanamide,

www.webofpharma.com

https://thuocngocanh.com/



D. (*RS*)-phenyl(pyridin-2-yl)acetonitrile (pyronitrile).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disopyramide Phosphate Capsules

General Notices

Action and use

Class I antiarrhythmic.

DEFINITION

Disopyramide Phosphate Capsules contain Disopyramide Phosphate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of disopyramide, $C_{21}H_{29}N_3O$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Suspend a quantity of the contents of the capsules containing the equivalent of 0.2 g of disopyramide in 50 mL of *chloroform*, add 2 mL of 13.5M *ammonia*, shake and filter through *anhydrous sodium sulfate*. Evaporate the filtrate to dryness using a rotary evaporator and dissolve the residue in 2 mL of *chloroform*. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of disopyramide *(RS 110)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution obtained in the Assay exhibits a maximum only at 269 nm and a shoulder at 263 nm.

C. Shake a quantity of the contents of the capsules containing the equivalent of 0.4 g of disopyramide with 20 mL of *water* and filter. The filtrate yields the reactions characteristic of *phosphates*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water* at a temperature of 37°, as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 262 nm, Appendix II B, using *water* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of disopyramide, $C_{21}H_{29}N_3O$, in the medium taking 125 as the value of A(1%, 1 cm) at the maximum at 262 nm.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing the equivalent of 0.20 g of disopyramide with 20 mL of *methanol* for 30 minutes and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia*, 30 volumes of *acetone* and 30 volumes of *cyclohexane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

To a quantity of the mixed contents of 20 capsules containing the equivalent of 40 mg of disopyramide, add 40 mL of 0.05M *methanolic sulfuric acid*, shake for 15 minutes, dilute to 100 mL with the same solvent and filter. Dilute 5 mL of the filtrate to 100 mL with 0.05M *methanolic sulfuric acid* and measure the *absorbance* of the resulting solution at the maximum at 269 nm, Appendix II B. Calculate the content of $C_{21}H_{29}N_3O$ taking 125 as the value of A(1%, 1 cm) at the maximum at 269 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of disopyramide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dispersible Cellulose

General Notices

Action and use

Pharmaceutical excipient.

DEFINITION

Dispersible Cellulose is a mixture of Microcrystalline Cellulose co-processed with Carmellose Sodium that readily forms a colloidal dispersion.

Content of carmellose sodium

75.0 to 125.0% w/w of the stated amount.

CHARACTERISTICS

A white or off-white, coarse or fine powder; hygroscopic.

Disperses in *water* producing a white, opaque dispersion or gel; practically insoluble in organic solvents and in dilute acids.

IDENTIFICATION

A. Mix 6 g with 300 mL of*water* stirring at 18,000 revolutions per minute for 5 minutes. A white, opaque dispersion is obtained which does not produce a supernatant liquid.

B. Add several drops of the dispersion obtained in test A to a 10% w/v solution of *aluminium chloride*. Each drop forms a white, opaque globule which does not disperse on standing.

C. Add 2 mL of *iodinated potassium iodide solution* to the dispersion obtained in test A. No blue or purplish colour is produced.

D. To the residue obtained in the test for Sulfated ash add 1 mL of *hydrochloric acid*, evaporate to dryness on a water bath and dissolve the residue in 20 mL of *water*. The resulting solution yields the reactions characteristic of *sodium salts*, Appendix VI, except that in test A the white precipitate produced may not be dense.

TESTS

Acidity or alkalinity

pH of the dispersion obtained in the test for Apparent viscosity, 6.0 to 8.0, Appendix V L.

Solubility

Add 50 mg to 10 mL of *ammoniacal solution of copper tetrammine* and shake. It dissolves completely leaving no residue.

www.webofpharma.com

https://thuocngocanh.com/

Apparent viscosity

60 to 140% of the declared value when determined by the following method. Calculate the quantity (*x* g) needed to prepare exactly 600 g of a dispersion of the stated percentage w/w, with reference to the dried substance. To (600-*x*) g of*water* at 23° to 25° contained in a 1000 mL high-speed blender bowl add *x* g of the substance being examined, stirring at reduced speed, taking care to avoid contacting the sides of the bowl with the powder. Continue stirring at low speed for 15 seconds after the addition and then stir at 18,000 revolutions per minute for exactly 2 minutes. Immerse the appropriate spindle of a rotational viscometer, switch on after 30 seconds and after a further 30 seconds determine the *viscosity*, Appendix V H, Method III, using a speed of 20 revolutions per minute (2.09 radians per second).

Loss on drying

When dried to constant weight at 105°, loses not more than 8.0% of its weight. Use 1 g.

Sulfated ash

Not more than 5.0%, Appendix IX A. Use 2 g.

ASSAY

Heat 2 g with 75 mL of *anhydrous acetic acid* under a reflux condenser for 2 hours, cool and carry out Method I for *non-aqueous titration*, Appendix VIII A, determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 29.6 mg of carmellose sodium.

STORAGE

Dispersible Cellulose should be protected from moisture.

LABELLING

The label states (1) the percentage w/w of Carmellose Sodium; (2) the viscosity of a dispersion in water of a stated percentage w/w of Carmellose Sodium.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

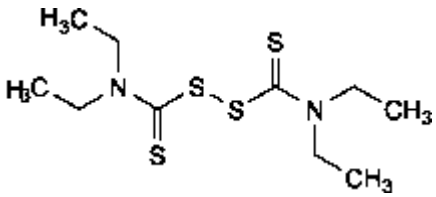
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Disulfiram

General Notices

(Ph. Eur. monograph 0603)



$C_{10}H_{20}N_2S_4$ 296.5 *97-77-8*

Action and use

Aldehyde dehyrogenase inhibitor; treatment of alcoholism.

Preparation

Disulfiram Tablets

Ph Eur

DEFINITION

Disulfiram contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of tetraethyldisulfanedicarbothioamide, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 70 °C to 73 °C.

www.webofpharma.com

https://thuocngocanh.com/

B. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with *disulfiram CRS*. Examine the substances prepared as discs.

C. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 10 mg in 10 mL of *methanol R*. Add 2 mL of a 0.5 g/L solution of *cupric chloride R* in *methanol R*. A yellow colour develops which becomes greenish-yellow.

TESTS

Related substances

Examine by thin-layer chromatography (2.2.27), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

Test solution (a) Dissolve 0.20 g of the substance to be examined in *ethyl acetate R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *ethyl acetate R*.

Reference solution (a) Dissolve 10 mg of *disulfiram CRS* in *ethyl acetate R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dilute 1 mL of test solution (b) to 20 mL with *ethyl acetate R*.

Apply to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 30 volumes of *butyl acetate R* and 70 volumes of *hexane R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Diethyldithiocarbamate

Dissolve 0.20 g in 10 mL of *peroxide-free ether R*, add 5 mL of *buffer solution pH 8.0 R* and shake vigorously. Discard the upper layer and wash the lower layer with 10 mL of *peroxide-free ether R*. Add to the lower layer 0.2 mL of a 4 g/L solution of *copper sulfate pentahydrate R* and 5 mL of *cyclohexane R*. Shake. Any yellow colour in the upper layer is not more intense than that of a standard prepared at the same time using 0.2 mL of a freshly prepared 0.15 g/L solution of *sodium diethyldithiocarbamate R* (150 ppm).

Loss on drying (2.2.32)

Not more than 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 50 °C.

Sulfated ash (2.4.14)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.450 g in 80 mL of *acetone R* and add 20 mL of a 20 g/L solution of *potassium nitrate R*. Titrate with *0.1 M silver nitrate*. Determine the end-point potentiometrically (2.2.20), using a silver electrode and a silver-silver chloride double-junction electrode saturated

www.webofpharma.com

https://thuocngocanh.com/

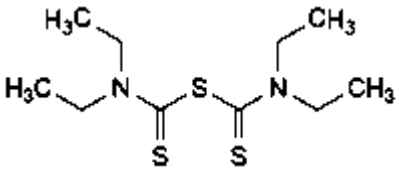
with potassium nitrate.

1 mL of *0.1 M silver nitrate* is equivalent to 59.30 mg of $C_{10}H_{20}N_2S_4$.

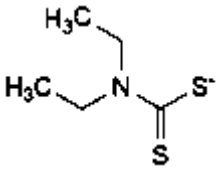
STORAGE

Store protected from light.

IMPURITIES



A. diethylthiocarbamic thioanhydride (sulfiram),



B. diethyldithiocarbamate.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Disulfiram Tablets

General Notices

Action and use

Aldehyde dehyrogenase inhibitor; treatment of alcoholism.

DEFINITION

Disulfiram Tablets contain Disulfiram.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of disulfiram, $C_{10}H_{20}N_2S_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 0.2 g of Disulfiram by shaking with 5 mL of *dichloromethane* and filter. Evaporate the filtrate to dryness and dry the residue at 40° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of disulfiram *(RS 111)*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (3).

C. Extract a quantity of the powdered tablets containing 0.3 g of disulfiram with *ethanol (96%)*, filter and evaporate the filtrate to dryness. Dissolve 50 mg of the residue in 5 mL of *ethanol (96%)* and add 1 mL of *potassium cyanide solution*. A yellow colour is produced which becomes green and then darkens to bluish green.

TESTS

Diethyldithiocarbamate

Shake a quantity of the powdered tablets containing 0.1 g of Disulfiram with 10 mL of *chloroform* and filter. Add 10 mL of 0.1M *sodium hydroxide* to the filtrate, shake, discard the chloroform layer and wash the aqueous layer with three 10 mL quantities of *chloroform*. To the aqueous layer add 0.25 mL of a 0.4% w/v solution of *copper(II) sulfate* and 2 mL of *dichloromethane*, shake and allow to separate. The lower layer is not more intensely coloured than a standard prepared at the same time and in the same manner by adding 10 mL of 0.1M *sodium hydroxide* to 0.2 mL of a freshly prepared 0.0075% w/v solution of *sodium diethyldithiocarbamate* and beginning at the words ‘add 0.25 mL of a 0.4% w/v solution of *copper(II) sulfate* ...’ (0.01%, calculated as the acid).

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 30 volumes of *butyl acetate* and 70 volumes of n-*hexane* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) extract a quantity of the powdered tablets containing 0.50 g of Disulfiram with 20 mL of *ethyl acetate* and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *ethyl acetate*. Solution (3) contains 0.025% w/v of *disulfiram BPCRS* in *ethyl acetate*. Solution (4) contains 0.050% w/v of *monosulfiram BPCRS* in *ethyl acetate*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to monosulfiram is not more intense than the spot in the chromatogram obtained with solution (4) (2%) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 0.4 g of Disulfiram add 75 mL of *methanol* and shake for 30 minutes. Add sufficient *methanol* to produce 100 mL, filter and dilute 5 mL of the filtrate to 100 mL with *methanol*. To 5 mL of this solution add sufficient of a 0.1% w/v solution of *copper(II) chloride* in *methanol* to produce 25 mL, mix and allow to stand for 1 hour. Measure the *absorbance* of the resulting solution at the maximum at 400 nm, Appendix II B, using in the reference cell a solution prepared by diluting 5 mL of *methanol* to 25 mL with the copper(II) chloride solution. Repeat the operation using 5 mL of a 0.020% w/v solution of *disulfiram BPCRS* in *methanol*, beginning at the words ‘add sufficient of a 0.1% w/v solution of *copper(II) chloride*…’. Calculate the content of $C_{10}H_{20}N_2S_4$ from the *absorbances* obtained and using the declared content of $C_{10}H_{20}N_2S_4$ in *disulfiram BPCRS*.

STORAGE

Disulfiram Tablets should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

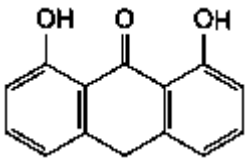
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dithranol

General Notices

(Ph. Eur. monograph 1007)



$C_{14}H_{10}O_3$ 226.2 *1143-38-0*

Action and use

Coal tar extract; treatment of psoriasis.

Preparations

Dithranol Cream

Dithranol Ointment

Dithranol Paste

Dithranol and Salicylic Acid Ointment

Ph Eur

DEFINITION

1,8-Dihydroxyanthracen-9(10*H*)-one.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow or brownish-yellow, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

Carry out all tests protected from bright light and use freshly prepared solutions.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Melting point (2.2.14): 178 °C to 182 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dithranol CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *dithranol CRS* in *methylene chloride R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve about 5 mg of *dantron R* (impurity B) in 5 mL of reference solution (a).

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *methylene chloride R* (50:50 *V/V*).

Application 10 µL.

Development Over a path of 12 cm.

Drying In air.

Detection Place the plate in a tank saturated with ammonia vapour until the spots appear. Examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To 5 mg add 0.1 g of *anhydrous sodium acetate R* and 1 mL of *acetic anhydride R*. Boil for 30 s. Add 20 mL of *ethanol (96 per cent) R*. Examined in ultraviolet light at 365 nm, the solution shows a blue fluorescence.

TESTS

Related substances

www.webofpharma.com

https://thuocngocanh.com/

A. Liquid chromatography (2.2.29).

Test solution Dissolve 0.200 g of the substance to be examined in 20 mL of methylene chloride R, add 1.0 mL of glacial acetic acid R and dilute to 100.0 mL with hexane R.

Reference solution Dissolve 5.0 mg of anthrone R (impurity A), 5.0 mg of dantron R (impurity B), 5.0 mg of dithranol impurity C CRS and 5.0 mg of dithranol CRS in methylene chloride R and dilute to 5.0 mL with the same solvent. To 1.0 mL of this solution, add 19.0 mL of methylene chloride R and 1.0 mL of glacial acetic acid R, and dilute to 50.0 mL with hexane R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: silica gel for chromatography R (5 µm).

Mobile phase glacial acetic acid R, methylene chloride R, hexane R (1:5:82 *V/V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL.

Run time 1.5 times the retention time of impurity C.

Elution order Dithranol, impurity B, impurity A, impurity C.

System suitability Reference solution:

— resolution: minimum 2.0 between the peaks due to dithranol and impurity B.

Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (1 per cent).

B. Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in 5 mL of tetrahydrofuran R and dilute to 25.0 mL with the mobile phase.

Reference solution Dissolve 5.0 mg of dithranol impurity D CRS and 5.0 mg of dithranol CRS in 5 mL of tetrahydrofuran R and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.20 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Mobile phase glacial acetic acid R, tetrahydrofuran R, water R (2.5:40:60 *V/V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 3 times the retention time of dithranol.

System suitability Reference solution:

— *resolution*: minimum 2.5 between the peaks due to impurity D and dithranol.

Limit:

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (2.5 per cent).

Total (tests A + B) Maximum 3.0 per cent for the sum of the contents of all impurities.

Chlorides (*2.4.4*)

Maximum 100 ppm.

Shake 1.0 g with 20 mL of *water R* for 1 min and filter. Dilute 10 mL of the filtrate to 15 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *anhydrous pyridine R*. Titrate with 0.1 M tetrabutylammonium hydroxide under *nitrogen R*. Determine the end-point potentiometrically (*2.2.20*), using a glass indicator electrode and a suitable reference electrode.

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 22.62 mg of $C_{14}H_{10}O_3$.

STORAGE

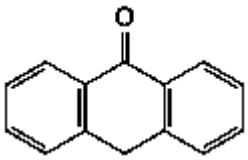
Protected from light.

IMPURITIES

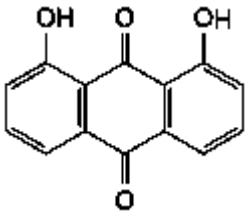
Specified impurities *A, B, C, D.*

www.webofpharma.com

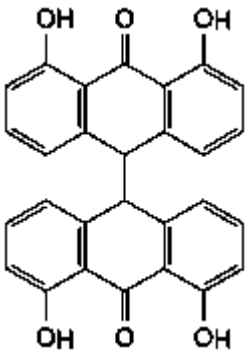
https://thuocngocanh.com/



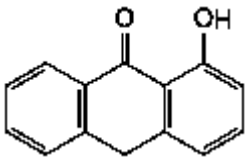
A. anthracen-9(10*H*)-one (anthrone),



B. 1,8-dihydroxyanthracene-9,10-dione (dantron),



C. 4,4′,5,5′-tetrahydroxy-9,9′-bianthracenyl-10,10′(9*H*,9′*H*)-dione,



D. 1-hydroxyanthracen-9(10*H*)-one.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dithranol and Salicylic Acid Ointment

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Coal tar extract; treatment of psoriasis.

DEFINITION

Dithranol and Salicylic Acid Ointment contains Dithranol and Salicylic Acid in a suitable emulsifying basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the ointment also complies with the requirements stated under Unlicensed Medicines.

Content of dithranol, $C_{14}H_{10}O_3$

90.0 to 110.0% of the stated amount.

Content of salicylic acid, $C_7H_6O_3$

90.0 to 110.0% of the stated amount of salicylic acid, corrected to account for the dithranol content.

IDENTIFICATION

A. In the Assay for Dithranol, the principal peak in the chromatogram obtained with solution (1) corresponds to the principal peak in the chromatogram obtained with solution (2).

B. Heat a quantity of the ointment containing 0.5 mg of Dithranol with 5 mL of 1M *sodium hydroxide* on a water bath with constant stirring. A pink colour is produced in the aqueous layer.

C. Shake 1 g with 10 mL of *water*, filter and add to the filtrate *iron(III) chloride solution R1*; an intense reddish violet colour is produced which persists on the addition of 6M *acetic acid*. Add *2M hydrochloric acid*; the colour disappears and a white, crystalline precipitate is produced.

TESTS

Impurities B and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing 20 mg of Dithranol in 20 mL of *dichloromethane*, add 1 mL of *glacial acetic acid*, dilute to 100 mL with *hexane* and filter through a fine glass microfibre filter paper (Whatman GF/C is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(2) Add 1 mL of *glacial acetic acid* to 20 mL of a solution containing 0.0050% w/v of *dantron BPCRS* (impurity B) and 0.0050% w/v of *dithranol impurity C EPCRS* (dimer) in *dichloromethane* and add sufficient *hexane* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Lichrosorb Si 60 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 380 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 5 volumes of *dichloromethane* and 82 volumes of *hexane*.

In the chromatogram obtained with solution (2), the substances elute in the following order: impurity B, impurity C.

LIMITS

Not more than 10.0% of the stated amount of dithranol, calculated as the sum of the amounts of impurities B and C. Calculate the amount of impurity B and impurity C in the ointment using the chromatograms obtained with solutions (1) and (2).

ASSAY

For dithranol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing 5 mg of Dithranol in 20 mL of *dichloromethane*, add 1 mL of *glacial acetic acid*, dilute to 100 mL with *hexane* and filter through a fine glass microfibre filter paper (Whatman GF/C is suitable).
(2) Add 1 mL of *glacial acetic acid* to 20 mL of a 0.025% w/v solution of *dithranol BPCRS* in *dichloromethane* and add sufficient *hexane* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Impurities B and C may be used but using a detection wavelength of 354 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{10}O_3$ in the ointment using the declared content of $C_{14}H_{10}O_3$ in *dithranol BPCRS*.

For salicylic acid

Carry out the method for *liquid chromatography*, Appendix III D, using the following freshly prepared solutions in amber glassware. Store and inject the solutions at 10°, using a cooled autosampler. Mix the ointment with a glass pestle for 5 minutes before analysis.

(1) Dissolve a quantity of the ointment containing 5 mg of Salicylic Acid in 20 mL of *dichloromethane* by shaking for 2 minutes and sonicating for 5 minutes. Add 1 mL of *glacial acetic acid*, dilute the solution with sufficient *hexane* to produce a solution containing 0.005% w/v of Salicylic Acid and filter through a 0.7-µm glass microfibre filter.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 10 volumes of a 0.05% w/v solution of *salicylic acid BPCRS* in a mixture of 1 volume of *glacial acetic acid*, 20 volumes of *dichloromethane* and 100 volumes of *hexane* to 100 volumes with the same mixture of solvents and filter through a 0.7-µm glass microfibre filter.

(3) Dilute 10 volumes of a 0.05% w/v solution of *dithranol BPCRS* in a mixture of 1 volume of *glacial acetic acid*, 20 volumes of *dichloromethane* and 100 volumes of *hexane* to 100 volumes with the same mixture of solvents and filter through a 0.7-µm glass microfibre filter.

(4) Equal volumes of solutions (2) and (3).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Spherisorb or Lichrosorb Si 60 are suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 302 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *glacial acetic acid*, 10 volumes of *dichloromethane* and 80 volumes of *hexane*.

Mobile phase B 2 volumes of *glacial acetic acid*, 10 volumes of *dichloromethane* and 80 volumes of *hexane*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	100	0	isocratic
5-6	100→50	0→50	linear gradient
6-10	50	50	isocratic
10-10.1	50→100	50→0	linear gradient
10.1-15	100	0	re-equilibration

SYSTEM SUITABILITY

The assay is not valid unless:

the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is less than 3.0;

in the chromatogram obtained with solution (4), the *resolution* between the peaks due to dithranol and salicylic acid is at least 8.0.

DETERMINATION OF CONTENT

Calculate the amount of $C_7H_6O_3$ in the ointment on the “as is” basis using the declared content of $C_7H_6O_3$ in *salicylic acid BPCRS* [A].

Adjust the stated amount of $C_7H_6O_3$ to account for the dithranol content, [B] using the following expression:

www.webofpharma.com

https://thuocngocanh.com/

$$B = C \times (100 - 2D) / 100$$

where,

C	=	stated amount of salicylic acid,
D	=	stated amount of dithranol.

Calculate the content of $C_7H_6O_3$ in the ointment relative to the corrected stated amount using the following expression:

$$(A \times 100) / B$$

STORAGE

Dithranol and Salicylic Acid Ointment should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B and C listed under Dithranol.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dithranol Cream

General Notices

Action and use

Coal tar extract; treatment of psoriasis.

DEFINITION

Dithranol Cream contains Dithranol in a suitable oil-in-water emulsified basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of dithranol, $C_{14}H_{10}O_3$

85.0 to 110.0% of the stated amount.

IDENTIFICATION

A. In the Assay the principal peak in the chromatogram obtained with solution (1) has the same retention time as that in the chromatogram obtained with solution (2).

B. Suspend a quantity of the cream containing 0.5 mg of dithranol in 5 mL of 1M *sodium hydroxide* and heat on a water bath for 1 minute while stirring. A pink colour is produced.

TESTS

Impurity B and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

For creams containing more than 0.5% w/v of Dithranol

(1) Disperse by shaking a quantity of the cream containing 50 mg of Dithranol in 10 mL of *glacial acetic acid* and 20 mL of *dichloromethane*. Filter through a glass microfibre filter paper (Whatman GF/C is suitable) into a 100-mL volumetric flask, wash the filter with *dichloromethane* and add sufficient *dichloromethane* to produce 100 mL. Shake the flask vigorously and allow to stand until two layers are obtained, add *dichloromethane* until the *dichloromethane* and *water* interface is level with the calibration mark, shake vigorously and allow to stand until two layers are obtained. Dilute 20 mL of the lower layer to 50 mL with *n-hexane*.

(2) Add 4 mL of *glacial acetic acid* to 20 mL of a solution containing 0.005% w/v of *dantron BPCRS* (impurity B) and 0.005% w/v of *dithranol impurity C EPCRS* in *dichloromethane* and add sufficient *n-hexane* to produce 100 mL.

For creams containing 0.5% w/v or less of Dithranol

www.webofpharma.com

https://thuocngocanh.com/

(1) Disperse by shaking a quantity of the cream containing 5 mg of Dithranol in 10 mL of *glacial acetic acid* and 20 mL of *dichloromethane*, filter through a glass microfibre filter paper (Whatman GF/C is suitable) into a 50-mL volumetric flask, wash the filter with *dichloromethane* and add sufficient *dichloromethane* to produce 50 mL. Shake the flask vigorously and allow to stand until two layers are obtained, add *dichloromethane* until the *dichloromethane* and *water* interface is level with the calibration mark, shake vigorously and allow to stand until two layers are obtained.

(2) Add 20 mL of *glacial acetic acid* to 10 mL of a solution containing 0.005% w/v of *dantron BPCRS* (impurity B) and 0.005% w/v of *dithranol impurity C EPCRS* in *dichloromethane* and add sufficient *dichloromethane* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used but using a detection wavelength of 380 nm.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to dithranol (retention time, about 4 minutes) are: impurity B, about 1.6; impurity C, about 4.0.

LIMITS

Not more than 10.0% of the stated amount of dithranol, calculated as the sum of the amounts of impurity B and C. Calculate the amounts of impurity B and impurity C in the cream with reference to the corresponding peaks in the chromatogram obtained with solution (2).

Impurity D

Carry out the method for *liquid chromatography*, Appendix III D, in subdued light using the following freshly prepared solutions.

(1) Disperse a quantity of the cream containing 10 mg of Dithranol in 30 mL of *water* at about 50°, add 30 mL of a warm, saturated solution of *sodium chloride*, cool and extract with three 40-mL quantities of *chloroform*. Filter the extract successively through *anhydrous sodium sulfate* on a suitable filter (Whatman GF/C is suitable). Evaporate the filtrate under reduced pressure to a volume of about 2 mL, add 25 mL of warm *methanol*, shake, cool in ice for 15 minutes and filter (Whatman GF/C paper is suitable). Evaporate the filtrate to dryness under reduced pressure and dissolve the residue in 10 mL of a mixture of 5 volumes of *glacial acetic acid* and 95 volumes of *acetonitrile*; filter if necessary.

(2) Dissolve 25 mg of *dithranol impurity D EPCRS* in 0.5 mL of *glacial acetic acid* and add sufficient *acetonitrile* to produce 50 mL. Dilute 1 mL of the resulting solution to 20 mL with *acetonitrile*.

(3) Dilute 1 volume of solution (1) to 40 mL with a mixture of 5 volumes of *glacial acetic acid* and 95 volumes of *acetonitrile*.

(4) Dissolve 50 mg of *dithranol BPCRS* in 0.5 mL of *glacial acetic acid*, add 2 mL of solution A and sufficient *acetonitrile* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 and Spherisorb ODS 2 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://nhathuocngocanh.com/

2.5 volumes of *glacial acetic acid*, 40 volumes of *tetrahydrofuran* and 60 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) closely resembles the chromatogram supplied with *dithranol BPCRS*.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to the principal peak in the chromatogram obtained with solution (2) is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (2.5%).

ASSAY

Carry out the following procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For creams containing more than 0.5% w/v of Dithranol

(1) Disperse by shaking a quantity of the cream containing 50 mg of Dithranol in 10 mL of *glacial acetic acid* and 20 mL of *dichloromethane*. Filter through a glass microfibre filter paper (Whatman GF/C is suitable) into a 100-mL volumetric flask, wash the filter with *dichloromethane* and add sufficient *dichloromethane* to produce 100 mL. Shake the flask vigorously and allow to stand until two layers are obtained, add *dichloromethane* until the *dichloromethane* and *water* interface is level with the calibration mark, shake vigorously and allow to stand until two layers are obtained. Dilute 20 mL of the lower layer to 50 mL with *n-hexane*. Dilute the resulting solution with *n-hexane* to produce a solution containing 0.002% w/v of Dithranol.

For creams containing 0.5% w/w or less of Dithranol

(1) Disperse by shaking a quantity of the cream containing 5 mg of Dithranol in 10 mL of *glacial acetic acid* and 20 mL of *dichloromethane*, filter through a glass microfibre filter paper (Whatman GF/C is suitable) into a 50-mL graduated flask, wash the filter with *dichloromethane* and add sufficient *dichloromethane* to produce 50 mL. Shake the flask vigorously and allow to stand until two layers are obtained, add *dichloromethane* until the *dichloromethane* and *water* interface is level with the calibration mark, shake vigorously and allow to stand until two layers are obtained. Dilute the mixture with *n-hexane* to contain 0.002% w/v of Dithranol.
(2) Add 1 mL of *glacial acetic acid* to 10 mL of a 0.02% w/v solution of *dithranol BPCRS* in *dichloromethane* and add sufficient of the mobile phase to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Lichrosorb Si 60 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 354 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 5 volumes of *dichloromethane* and 82 volumes of *n-hexane*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{10}O_3$ in the cream using the declared content of $C_{14}H_{10}O_3$ in *dithranol BPCRS*.

STORAGE

Dithranol Cream should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C, and D listed under Dithranol.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dithranol Ointment

General Notices

Action and use

Coal tar extract; treatment of psoriasis.

DEFINITION

Dithranol Ointment contains Dithranol, in *fine powder*, in a suitable hydrophobic basis.

Extemporaneous preparation

The following directions apply.

Triturate Dithranol, in *fine powder*, with Yellow Soft Paraffin, add sufficient Yellow Soft Paraffin to produce an ointment of the required strength and mix thoroughly. Part of the Yellow Soft Paraffin may be replaced by Hard Paraffin to produce an ointment of stiffer consistency.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the ointment also complies with the requirements stated under Unlicensed Medicines.

Content of dithranol, $C_{14}H_{10}O_3$

85.0 to 110.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

B. Heat a quantity of the ointment containing 0.5 mg of Dithranol with 5 mL of 1M *sodium hydroxide* on a water bath with constant stirring. A pink colour is produced in the aqueous layer.

TESTS

Impurities B and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing 20 mg of Dithranol in 20 mL of *dichloromethane*, add 1 mL of *glacial acetic acid*, dilute to 100 mL with *hexane* and filter through a fine glass microfibre filter paper (Whatman GF/C is suitable).

(2) Add 1 mL of *glacial acetic acid* to 20 mL of a solution containing 0.0050% w/v of *dantron BPCRS* (impurity B) and 0.0050% w/v of *dithranol impurity C EPCRS* (dimer) in *dichloromethane* and add sufficient *hexane* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Lichrosorb Si 60 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 380 nm.

(f) Inject 20 µL of each solution.

In the chromatogram obtained with solution (2), the substances elute in the following order: impurity B, impurity C.

MOBILE PHASE

1 volume of *glacial acetic acid*, 5 volumes of *dichloromethane* and 82 volumes of *hexane*.

LIMITS

Not more than 10.0% of the stated amount of dithranol, calculated as the sum of the amounts of impurities B and C. Calculate the amount of impurity B and impurity C in the ointment using the chromatograms obtained with solutions (1) and (2).

Impurity D

Carry out the method for *liquid chromatography*, Appendix III D, in subdued light using the following freshly prepared solutions.

(1) Disperse a quantity of the ointment containing 10 mg of Dithranol in 25 mL of *chloroform*, evaporate under reduced pressure to a volume of about 2 mL, add 25 mL of warm *methanol*, shake, cool in ice for 15 minutes and filter (Whatman GF/C paper is suitable). Evaporate the filtrate to dryness under reduced pressure and dissolve the residue in 10 mL of a mixture of 5 volumes of *glacial acetic acid* and 95 volumes of *acetonitrile*; filter if necessary.

(2) Dissolve 25 mg of *dithranol impurity D EPCRS* (1-hydroxy-9-anthrone) in 0.5 mL of *glacial acetic acid* and add sufficient *acetonitrile* to produce 50 mL (solution A); dilute 1 mL of solution A to 20 mL with *acetonitrile*.

(3) Dilute 1 volume of solution (1) to 40 mL with a mixture of 5 volumes of *glacial acetic acid* and 95 volumes of *acetonitrile*.

(4) Dissolve 50 mg of *dithranol BPCRS* in 0.5 mL of *glacial acetic acid*, add 2 mL of solution A and sufficient *acetonitrile* to produce 50 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 and Spherisorb ODS 2 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

2.5 volumes of *glacial acetic acid*, 40 volumes of *tetrahydrofuran* and 60 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) closely resembles the reference chromatogram supplied with *dithranol BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D, identified from the chromatogram obtained with solution (2), is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (2.5%).

ASSAY

Carry out the following procedure protected from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing 5 mg of Dithranol in 20 mL of *dichloromethane*, add 1 mL of *glacial acetic acid*, dilute to 100 mL with *hexane* and filter through a fine glass microfibre filter paper (Whatman GF/C is suitable).
(2) Add 1 mL of *glacial acetic acid* to 20 mL of a 0.025% w/v solution of *dithranol BPCRS* in *dichloromethane* and add sufficient *hexane* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Impurities B and C may be used but using a detection wavelength of 354 nm.

MOBILE PHASE

1 volume of *glacial acetic acid*, 5 volumes of *dichloromethane* and 82 volumes of *hexane*.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{10}O_3$ in the ointment using the declared content of $C_{14}H_{10}O_3$ in *dithranol BPCRS*.

STORAGE

Dithranol Ointment should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C and D listed under Dithranol.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dithranol Paste

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Coal tar extract; treatment of psoriasis.

DEFINITION

Dithranol Paste contains Dithranol in a suitable hydrophobic basis containing Zinc Oxide and Salicylic Acid.

The paste complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the paste also complies with the requirements stated under Unlicensed Medicines.

Content of dithranol, $C_{14}H_{10}O_3$

85.0 to 110.0% of the stated amount.

Content of salicylic acid, $C_7H_6O_3$

93.0 to 107.0% of the stated amount.

Content of zinc oxide, ZnO

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay for dithranol, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

B. Suspend a quantity of the paste containing 0.5 mg of Dithranol in 5 mL of 1M *sodium hydroxide* and heat on a water bath for 1 minute while stirring. A pink colour is produced.

C. Disperse 0.5 g of the paste in 10 mL of *chloroform*, filter, extract the filtrate with 10 mL of a 1% w/v solution of *sodium hydrogen carbonate* and wash the extract with 5 mL of *chloroform*. To 5 mL add 3 mL of *iron(III) chloride solution R1*. A violet colour is produced which persists after the addition of 0.5 mL of 5M *acetic acid*.

TESTS

Impurities B and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Disperse a quantity of the paste containing 20 mg of Dithranol in 20 mL of *dichloromethane* with warming and stirring, centrifuge and decant the supernatant layer into a 100-mL flask. Disperse the residue in 20 mL of *hexane*, centrifuge, decant the supernatant layer into the 100-mL flask and repeat the procedure with a further two 20-mL quantities of *hexane*. Add 1 mL of *glacial acetic acid* to the combined extracts, dilute to 100 mL with *hexane* and filter through a fine glass microfibre filter paper (Whatman GF/C paper is suitable).

(2) Add 1 mL of *glacial acetic acid* to 20 mL of a solution containing 0.0050% w/v of *dantron BPCRS* (impurity B) and 0.0050% w/v of *dithranol impurity C BPCRS* (dimer) in *dichloromethane* and add sufficient *hexane* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Lichrosorb Si 60 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 380 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 5 volumes of *dichloromethane* and 82 volumes of *hexane*.

In the chromatogram obtained with solution (2), the substances elute in the following order: impurity B, impurity C.

LIMITS

Not more than 10.0% of the stated amount of dithranol, calculated as the sum of the amounts of impurities B and C. Calculate the amount of impurity B and impurity C in the paste using the chromatograms obtained with solutions (1) and (2).

ASSAY

For dithranol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the paste containing 5 mg of Dithranol in 20 mL of *dichloromethane* with warming and stirring, centrifuge and decant the supernatant layer into a 100-mL flask. Disperse the residue in 20 mL of *hexane*, centrifuge, decant the supernatant layer into the 100-mL flask and repeat the procedure with a further two 20-mL quantities of *hexane*. Add 1 mL of *glacial acetic acid* to the combined extracts, dilute to 100 mL with *hexane* and filter through a fine glass microfibre filter paper (Whatman GF/C is suitable).

(2) Add 1 mL of *glacial acetic acid* to 20 mL of a 0.025% w/v solution of *dithranol BPCRS* in *dichloromethane* and add sufficient *hexane* to produce 100 mL.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Impurities B and C may be used but using a detection wavelength of 354 nm.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{10}O_3$ in the paste using the declared content of $C_{14}H_{10}O_3$ in *dithranol BPCRS*.

For salicylic acid

www.webofpharma.com

https://thuocngocanh.com/

Shake 0.5 g with 10 mL of 1M *hydrochloric acid* and 10 mL of *ether* until fully dispersed. Decant and reserve the aqueous layer. Extract the ether layer with two further 10-mL quantities of 1M *hydrochloric acid*, combine the aqueous extracts with the reserved aqueous layer, wash with 10 mL of *ether* and reserve for the Assay for zinc oxide. Combine the ether extract and washings, add 15 mL of *petroleum spirit (boiling range, 40° to 60°)* and extract with successive quantities of 20 mL, 10 mL and 10 mL of *borate buffer pH 9.0*. Dilute the combined extracts to 100 mL with 2M *hydrochloric acid*, dilute 15 mL of the resulting solution to 50 mL with the same solvent and measure the *absorbance* of the final solution at the maximum at 302 nm, Appendix II B. Calculate the content of $C_7H_6O_3$ in the paste taking 260 as the value of A(1%, 1 cm) at the maximum at 302 nm.

For zinc oxide

To the combined aqueous extracts obtained in the Assay for salicylic acid add 20 mL of 1M *sodium hydroxide* and 50 mg of *xylenol orange triturate*. To the resulting solution add sufficient *hexamine* to change the colour of the solution to red, and then a further 3 g of *hexamine*, and titrate with 0.1M *disodium edetate VS*. Each mL of 0.1M *disodium edetate VS* is equivalent to 8.137 mg of ZnO.

STORAGE

Dithranol Paste should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B and C listed under Dithranol.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

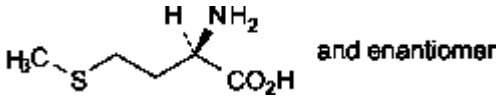
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

DL-Methionine

General Notices

(Ph. Eur. monograph 0624)



$C_5H_{11}NO_2S$ 149.2 *59-51-8*

Action and use

Used in treatment of paracetamol overdose.

Ph Eur

DEFINITION

DL-Methionine contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (2*RS*)-2-amino-4-(methylsulfanyl)butanoic acid, calculated with reference to the dried substance.

CHARACTERS

Almost white, crystalline powder or small flakes, sparingly soluble in water, very slightly soluble in ethanol (96 per cent). It dissolves in dilute acids and in dilute solutions of the alkali hydroxides.

It melts at about 270 °C (instantaneous method).

IDENTIFICATION

First identification: A, C.

Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *DL-methionine CRS*. Dry the substances at 105 °C.

B. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

C. Dissolve 2.50 g in *1 M hydrochloric acid* and dilute to 50.0 mL with the same acid. The angle of optical rotation (*2.2.7*) is -0.05° to + 0.05°.

D. Dissolve 0.1 g of the substance to be examined and 0.1 g of *glycine R* in 4.5 mL of *dilute sodium hydroxide solution R*. Add 1 mL of a 25 g/L solution of *sodium nitroprusside R*. Heat to 40 °C for 10 min. Allow to cool and add 2 mL of a mixture of 1 volume of *phosphoric acid R* and 9 volumes of *hydrochloric acid R*. A deep-red colour develops.

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

The pH of solution S is 5.4 to 6.1.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a) Dissolve 0.2 g in *water R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 50 mL with *water R*.

Reference solution (a) Dissolve 20 mg of *DL-methionine CRS* in *water R* and dilute to 50 mL with the same solvent.

Reference solution (b) Dilute 1 mL of reference solution (a) to 10 mL with *water R*.

Apply separately to the plate 5 µL of each solution. Develop over a path of 10 cm using a mixture of 20 volumes of *glacial acetic acid R*, 20 volumes of *water R* and 60 volumes of *butanol R*. Allow the plate to dry in air and spray with *ninhydrin solution R*. Heat the plate at 100 °C to 105 °C for 15 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Chlorides

Dissolve 0.25 g in 35 mL of *water R*. Add 5 mL of *dilute nitric acid R* and 10 mL of *silver nitrate solution R2*. Allow to stand protected from light for 5 min. Any opalescence in the solution is not more intense than that in a standard prepared at the same time in the same manner using a mixture of 10 mL of *chloride standard solution (5 ppm Cl) R* and 25 mL of *water R* (200 ppm). Examine the tubes laterally against a black background.

Sulfates (*2.4.13*)

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 1.0 g in 20 mL of *distilled water R*, heating to 60 °C. Cool to 10 °C and filter. 15 mL of the solution complies with the limit test for sulfates (200 ppm).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.140 g in 3 mL of *anhydrous formic acid R*. Add 30 mL of *anhydrous acetic acid R*. Immediately after dissolution, titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 14.92 mg of $C_5H_{11}NO_2S$.

STORAGE

Store protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

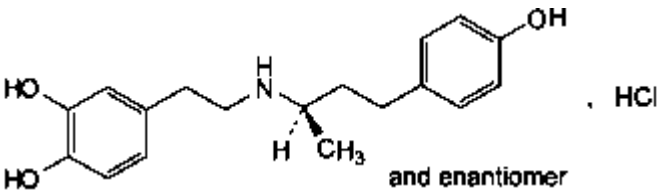
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dobutamine Hydrochloride

General Notices

(Ph. Eur. monograph 1200)



$C_{18}H_{24}ClNO_3$ 337.8 *49745-95-1*

Action and use

Beta$_1$-adrenoceptor agonist.

Preparation

Dobutamine Infusion

Ph Eur

DEFINITION

4-[2-[[(2*RS*)-4-(4-Hydroxyphenyl)-butan-2-yl]amino]ethyl]benzene-1,2-diol hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *dobutamine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*) using a mixture of equal volumes of *methanol R* and *water R*.

TESTS

Acidity or alkalinity

Dissolve 0.1 g in *water R* with gentle heating and dilute to 10 mL with the same solvent. Add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Absorbance (*2.2.25*)

Maximum 0.04 at 480 nm.

Dissolve 0.5 g in a mixture of equal volumes of *methanol R* and *water R* with heating, if necessary, at 30-35 °C and dilute to 25 mL with the same mixture of solvents. Cool quickly. Examine immediately.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Mobile phase B, mobile phase A (35:65 *V/V*).

Test solution Dissolve 0.10 g of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 4.0 mL of the test solution to 100.0 mL with a 0.05 g/L solution of *anisaldehyde R* in the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *dobutamine impurity mixture CRS* (impurities A, B and C) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 2.60 g of *sodium octanesulfonate R* in 1000 mL of *water R*, add 3 mL of *triethylamine R* and adjust to pH 2.5 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*, *methanol R* (18:82 *V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	65	35
5 - 20	65 → 20	35 → 80
20 - 25	20	80

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *dobutamine impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

Relative retention With reference to dobutamine (retention time = about 12 min): impurity A = about 0.3; impurity B = about 0.5; anisaldehyde = about 0.7; impurity C = about 1.4.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to dobutamine and anisaldehyde.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 1.4;

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.250 g in 10 mL of *anhydrous formic acid R*. Add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

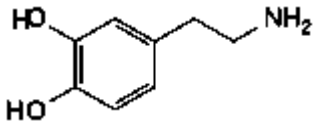
1 mL of *0.1 M perchloric acid* is equivalent to 33.79 mg of $C_{18}H_{24}ClNO_3$.

STORAGE

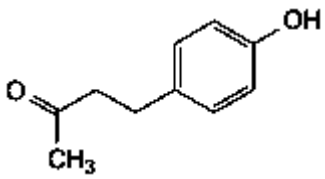
Protected from light.

IMPURITIES

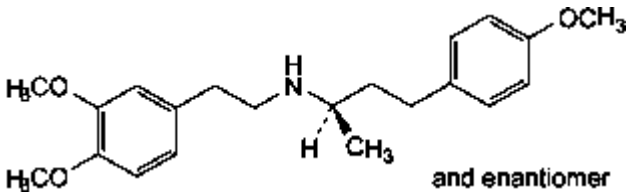
Specified impurities *A, B, C.*



A. 4-(2-aminoethyl)benzene-1,2-diol (dopamine),



B. 4-(4-hydroxyphenyl)butan-2-one,



C. (2*RS*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-4-(4-methoxyphenyl)butan-2-amine.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dobutamine Infusion

General Notices

Dobutamine Intravenous Infusion

Action and use

Beta$_1$-adrenoceptor agonist.

DEFINITION

Dobutamine Infusion is a sterile solution containing Dobutamine Hydrochloride. It is supplied as a ready-to-use solution or it is prepared by diluting either Dobutamine Sterile Concentrate or Dobutamine Hydrochloride for Injection with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

TESTS

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C, Method D. Dilute the infusion, if necessary, with *water BET* to give a solution containing the equivalent of 10 mg of dobutamine per mL (solution A). The endotoxin limit concentration of solution A is 10 IU per mL.

STORAGE

Dobutamine Infusion prepared from Sterile Dobutamine Concentrate or from Dobutamine Hydrochloride for Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

When supplied as a ready-to-use solution, the infusion complies with the following requirements.

Content of dobutamine, $C_{18}H_{23}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Use the infusion being examined diluted, if necessary, in a mixture of 1 volume of *water* and 4 volumes of *methanol* to produce a solution containing the equivalent of 0.05% w/v of dobutamine.

(2) 0.05% w/v of *dobutamine hydrochloride BPCRS* in a mixture of 1 volume of *water* and 4 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* precoated plate.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and spray with a 0.5% w/v solution of *potassium permanganate* in 1M *sodium hydroxide*.

MOBILE PHASE

2 volumes of *water*, 6 volumes of *glacial acetic acid*, 12 volumes of *ether* and 18 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

Related substances

Complies with the test described in the requirements for Sterile Dobutamine Concentrate but using the following solutions.

(1) Use the infusion diluted, if necessary, with a mixture of equal volumes of mobile phase A and mobile phase B to produce a solution containing the equivalent of 0.05% w/v of dobutamine.

(2) Dilute 4 volumes of solution (1) to 100 volumes with a 0.0005% w/v solution of *anisaldehyde* in a mixture of equal volumes of mobile phase A and mobile phase B and dilute 1 volume of the solution to 10 volumes with the same mixture of mobile phases.

(3) Dilute 1 volume of solution (1) to 100 volumes with a mixture of equal volumes of mobile phase A and mobile phase B.

ASSAY

Carry out the Assay described under the requirements for Sterile Dobutamine Concentrate but for solution (1) use the infusion being examined diluted, if necessary, with the mobile phase to contain the equivalent of 0.05% w/v of dobutamine.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of dobutamine.

DOBUTAMINE STERILE CONCENTRATE

DEFINITION

Dobutamine Sterile Concentrate is a sterile solution of Dobutamine Hydrochloride in Water for Injections.

www.webofpharma.com

https://thuocngocanh.com/

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of dobutamine, $C_{18}H_{23}NO_3$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or pale yellow solution.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Use the concentrate being examined diluted, if necessary, with *water* to produce a solution containing the equivalent of 1.25% w/v of dobutamine.

(2) 1.25% w/v of *dobutamine hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel 60 F_{254}* precoated plate.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. Spray the plate with a 6.0% w/v solution of *iron(III) chloride hexahydrate* and then with a 2% w/v solution of *potassium hexacyanoferrate(III)*.

MOBILE PHASE

5 volumes of *glacial acetic acid*, 15 volumes of *water*, 40 volumes of *propan-1-ol* and 100 volumes of *ethyl acetate*.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of the concentrate diluted, if necessary, to contain the equivalent of 1.25% w/v of dobutamine, 2.5 to 4.0, Appendix V L.

Clarity of solution

Dilute the concentrate, if necessary, to contain the equivalent of 1.25% w/v of dobutamine. The solution is not more opalescent than *reference suspension I*, Appendix IV A.

www.webofpharma.com

https://thuocngocanh.com/

Light absorption

The *light absorption*, Appendix II B, at 400 nm of the concentrate diluted, if necessary, to contain the equivalent of 1.25% w/v of dobutamine is not more than 0.20.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the concentrate with a mixture of equal volumes of mobile phase A and mobile phase B to produce a solution containing the equivalent of 0.5% w/v of dobutamine.
(2) Dilute 4 volumes of solution (1) to 100 volumes with a 0.005% w/v solution of *anisaldehyde* in a mixture of equal volumes of mobile phase A and mobile phase B and dilute 1 volume of the solution to 10 volumes with the same mixture of mobile phases.
(3) Dilute 1 volume of solution (1) to 100 volumes with a mixture of equal volumes of mobile phase A and mobile phase B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 2.60 g of *sodium octanesulfonate* in 1000 mL of *water* and add 3 mL of *triethylamine*; adjust to pH 2.5 with *orthophosphoric acid*.

Mobile phase B 18 volumes of *acetonitrile* and 82 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	65	35	isocratic
5-20	65→20	35→80	linear gradient
20-25	20	80	isocratic
25-26	20→65	80→35	linear gradient
26-35	65	35	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks corresponding to dobutamine and anisaldehyde is at least 4.0.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the concentrate with the mobile phase to produce a solution containing the equivalent of 0.05% w/v of dobutamine.
(2) 0.06% w/v of *dobutamine hydrochloride BPCRS* in the mobile phase.
(3) 0.06% w/v of *dobutamine hydrochloride BPCRS* and 0.03% w/v of *4-(4-hydroxyphenyl)butan-2-one* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

14 volumes of *methanol*, 28 volumes of *acetonitrile* and 58 volumes of a solution prepared by dissolving 3.38 g of *sodium octanesulfonate* in 1000 mL of *water*, adding 3 mL of *triethylamine* and adjusting the pH to 2.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dobutamine and 4-(4-hydroxyphenyl)butan-2-one is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{23}NO_3$ in the concentrate from the chromatograms obtained using the declared content of $C_{18}H_{23}NO_3$ in *dobutamine hydrochloride BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of dobutamine.

DOBUTAMINE HYDROCHLORIDE FOR INJECTION

www.webofpharma.com

https://thuvienthuocngocanh.com/

DEFINITION

Dobutamine Hydrochloride for Injection is a sterile material consisting of Dobutamine Hydrochloride with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of dobutamine, $C_{18}H_{23}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve the contents of the sealed container in sufficient of a mixture of 1 volume of *water* and 4 volumes of *methanol* to produce a solution containing the equivalent of 1.0% w/v of dobutamine.

(2) 1% w/v of *dobutamine hydrochloride BPCRS* in a mixture of 1 volume of *water* and 4 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* precoated plate.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and spray with a 0.5% w/v solution of *potassium permanganate* in 1M *sodium hydroxide*.

MOBILE PHASE

2 volumes of *water*, 6 volumes of *glacial acetic acid*, 12 volumes of *ether* and 18 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of a solution containing the equivalent of 2.5% w/v of dobutamine, 2.5 to 4.5, Appendix V L.

Clarity of solution

A solution containing the equivalent of 2.5% w/v of dobutamine is not more opalescent than *reference suspension II*, Appendix IV A.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Light absorption

The *absorbance*, Appendix II B, at 480 nm of a solution containing the equivalent of 2.5% w/v of dobutamine is not more than 0.065.

Related substances

Comply with the test described in the requirements for Sterile Dobutamine Concentrate but preparing solution (1) in the following manner. Dissolve the contents of the sealed container in a mixture of equal volumes of mobile phase A and mobile phase B to produce a solution containing the equivalent of 0.5% w/v of dobutamine.

Water

Not more than 2.0%, Appendix IX C. Use the contents of a single container and add 7 g of *salicylic acid* and 20 mL of *formamide* before the determination.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve the contents of one container in the mobile phase to produce a solution containing the equivalent of 0.05% w/v of dobutamine.
(2) 0.06% w/v of *dobutamine hydrochloride BPCRS* in the mobile phase.
(3) 0.06% w/v of *dobutamine hydrochloride BPCRS* and 0.03% w/v of *4-(4-hydroxyphenyl)butan-2-one* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay in the requirements for Sterile Dobutamine Concentrate may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dobutamine and 4-(4-hydroxyphenyl)butan-2-one is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{23}NO_3$ in the container using the declared content of $C_{18}H_{23}NO_3$ in *dobutamine hydrochloride BPCRS*.

Repeat the procedure on the contents of a further two containers. Determine the content of $C_{18}H_{23}NO_3$ using the average of the three individual results obtained.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of dobutamine.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

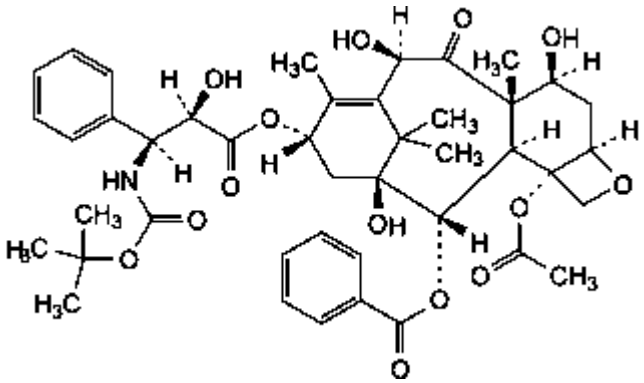
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Docetaxel

General Notices

Anhydrous Docetaxel

(Ph. Eur. monograph 2593)



$C_{43}H_{53}NO_{14}$ 808 *114977-28-5*

Action and use

Taxane cytotoxic.

Ph Eur

DEFINITION

5β,20-Epoxy-1,7β,10β-trihydroxy-9-oxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate].

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline, hygroscopic powder.

Solubility

Practically insoluble in water, freely soluble in anhydrous ethanol, soluble in methylene chloride.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *anhydrous docetaxel CRS*.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution B_5 (2.2.2, *Method I*).

Dissolve 1.0 g in *anhydrous ethanol R* and dilute to 20 mL with the same solvent.

Specific optical rotation (2.2.7)

-41.5 to -38.5 (anhydrous substance).

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetic acid R*, *acetonitrile R1*, *water R* (0.05:50:50 *V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of *docetaxel trihydrate CRS* in 2.5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *docetaxel for system suitability CRS* (containing impurities A, B and C) in 0.25 mL of *anhydrous ethanol R* and dilute to 5.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of *docetaxel impurity E CRS* in 2.5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: *water R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	72	28
9 - 39	72 → 28	28 → 72

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 232 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *docetaxel for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity E.

Relative retention With reference to docetaxel (retention time = about 27 min): impurity E = about 0.2; impurity A = about 0.97; impurity B = about 1.08; impurity C = about 1.13.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to impurity A and docetaxel.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.6;

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurity E*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.15 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: maximum 0.8 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.32)

Maximum 1.5 per cent.

Inject 800 µL of a 25 mg/mL solution of the substance to be examined in *methanol R*.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (2.6.14)

Less than 0.3 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 10 µL of the test solution and reference solution (a).

Calculate the percentage content of $C_{43}H_{53}NO_{14}$ taking into account the assigned content of *docetaxel trihydrate CRS*.

STORAGE

Protected from light, in an airtight container.

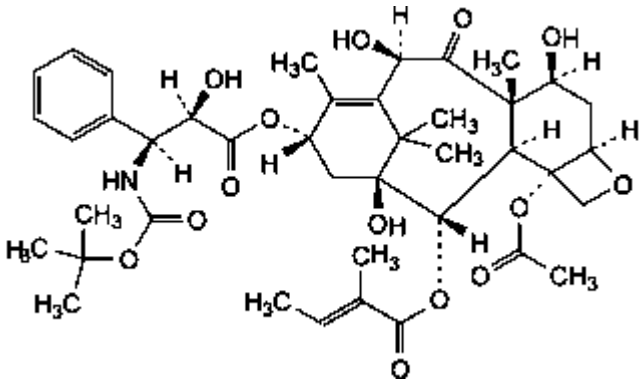
IMPURITIES

Specified impurities *A, B, C, E.*

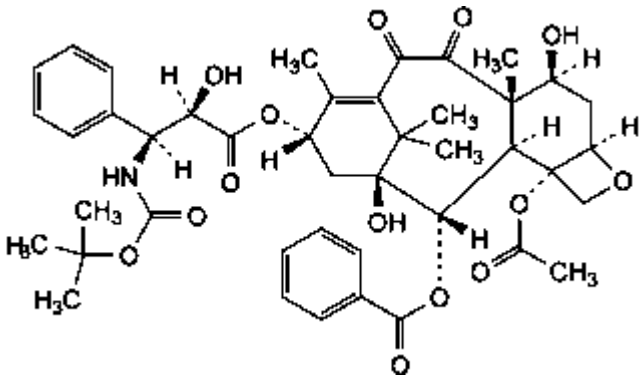
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, F, G.*

www.webofpharma.com

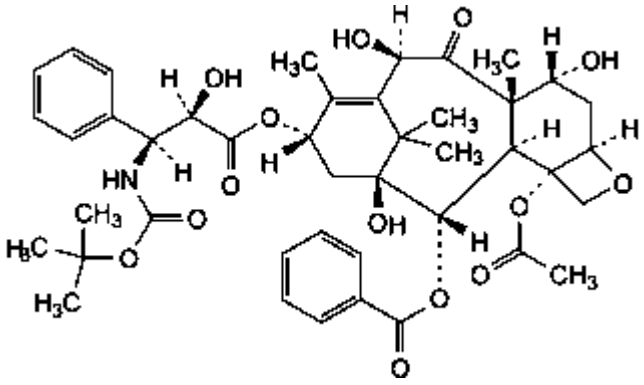
https://thuocngocanh.com/



A. 5β,20-epoxy-1,7β,10β-trihydroxy-9-oxotax-11-ene-2α,4,13α-triyl 4-acetate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] 2-[(2*E*)-2-methylbut-2-enoate] (2-*O*-desbenzoyl-2-*O*-tiglyldocetaxel),



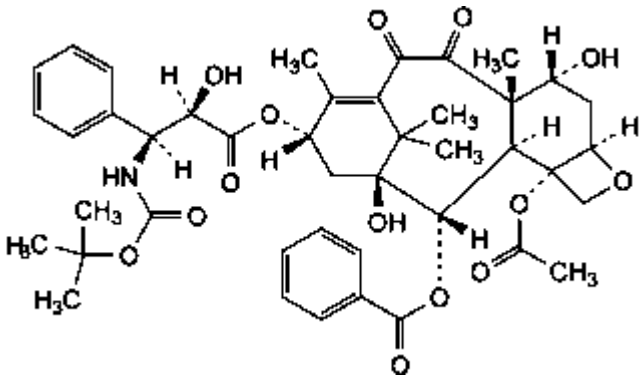
B. 5β,20-epoxy-1,7β-dihydroxy-9,10-dioxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] (10-deoxy-10-oxodocetaxel),



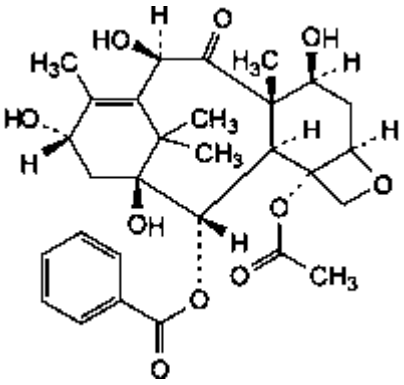
C. 5β,20-epoxy-1,7α,10β-trihydroxy-9-oxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] (7-*epi*-docetaxel),

www.webofpharma.com

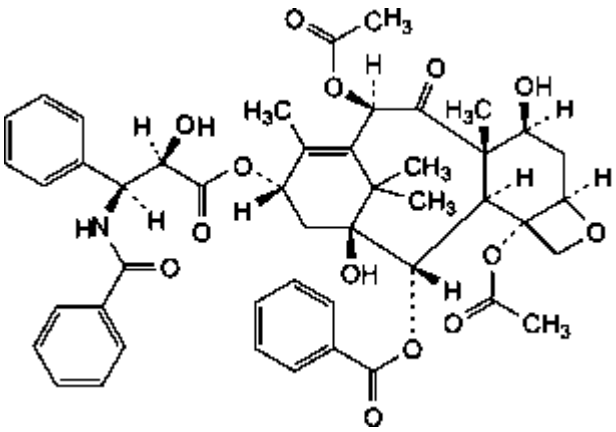
https://thuocngocanh.com/



D. 5β,20-epoxy-1,7α-dihydroxy-9,10-dioxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] (10-deoxy-10-oxo-7-*epi*-docetaxel),



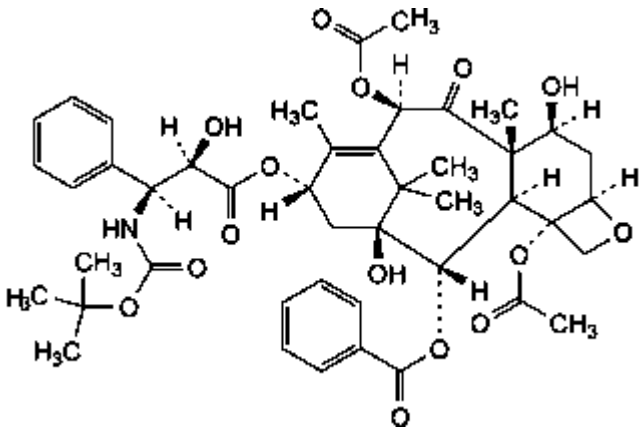
E. 5β,20-epoxy-4-(acetyloxy)-1,7β,10β,13α-tetrahydroxy-9-oxotax-11-en-2α-yl benzoate (10-desacetyl-baccatin III),



F. 5β,20-epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2*R*,3*S*)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate] (paclitaxel),

www.webofpharma.com

https://thuocngocanh.com/



G. 5β,20-epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] (10-acetyldocetaxel).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

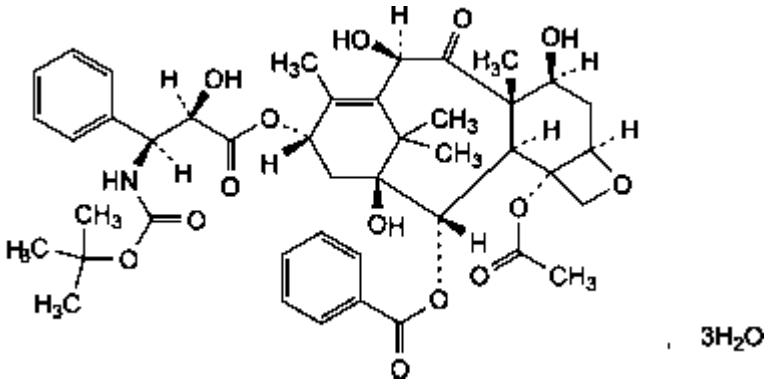
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Docetaxel Trihydrate

General Notices

(Ph. Eur. monograph 2449)



$C_{43}H_{53}NO_{14},3H_2O$ 862 *148408-66-6*

Action and use

Taxane cytotoxic.

Ph Eur

DEFINITION

5β,20-epoxy-1,7β,10β-Trihydroxy-9-oxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] trihydrate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in anhydrous ethanol, soluble in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *docetaxel trihydrate CRS*.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution B_5 (2.2.2, *Method I*).

Dissolve 1.0 g in *anhydrous ethanol R* and dilute to 20 mL with the same solvent.

Specific optical rotation (2.2.7)

-41.5 to -38.5 (anhydrous substance).

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetic acid R*, *acetonitrile R1*, *water R* (0.05:50:50 *V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of *docetaxel trihydrate CRS* in 2.5 mL of *anhydrous ethanol R* and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *docetaxel for system suitability CRS* (containing impurities A, B and C) in 0.25 mL of *anhydrous ethanol R* and dilute to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: *water R*;

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	72	28
9 - 39	72 → 28	28 → 72

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 232 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *docetaxel for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

Relative retention With reference to docetaxel (retention time = about 27 min): impurity A = about 0.97; impurity B = about 1.08; impurity C = about 1.13.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to impurity A and docetaxel.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.6;

— *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities B, C*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.32*)

5.0 per cent to 7.0 per cent.

Inject 200 µL of a 100 mg/mL solution of the substance to be examined in *dimethylformamide R*.

Sulfated ash (*2.4.14*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.3 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 10 µL of the test solution and reference solution (a).

Calculate the percentage content of $C_{43}H_{53}NO_{14}$ taking into account the assigned content of *docetaxel trihydrate CRS*.

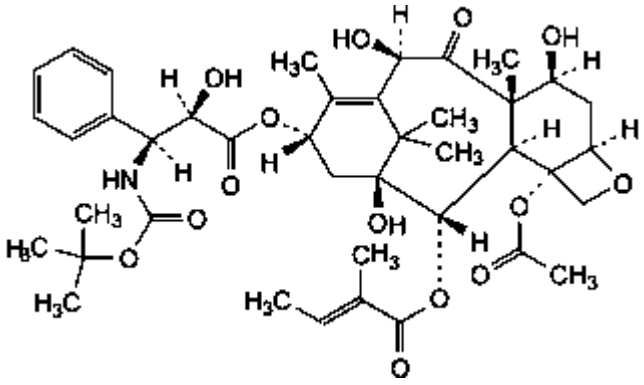
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C.*

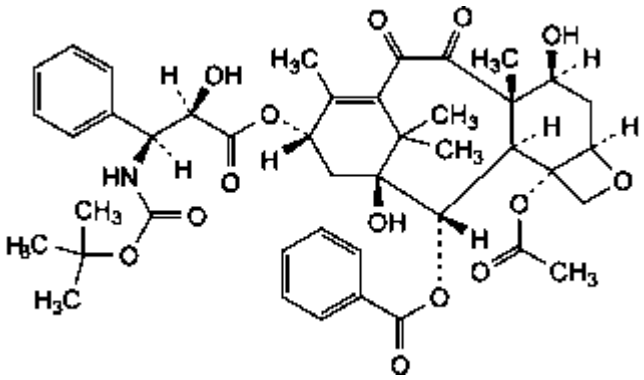
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*



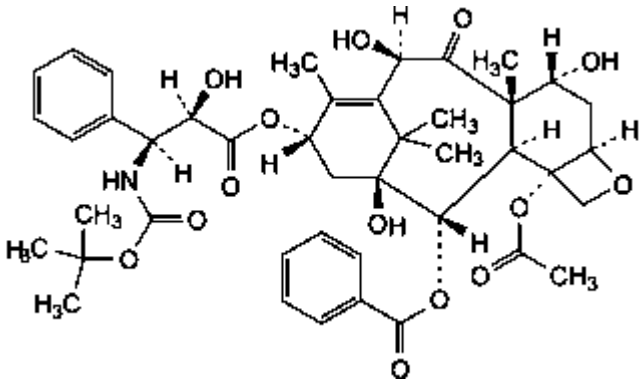
A. 5β,20-epoxy-1,7β,10β-trihydroxy-9-oxotax-11-ene-2α,4,13α-triyl 4-acetate 13-[(2*R*,3*S*)-3-[[(1,1dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] 2-[(2*E*)-2-methylbut-2-enoate] (2-*O*-desbenzoyl-2-*O*-tiglyldocetaxel),

www.webofpharma.com

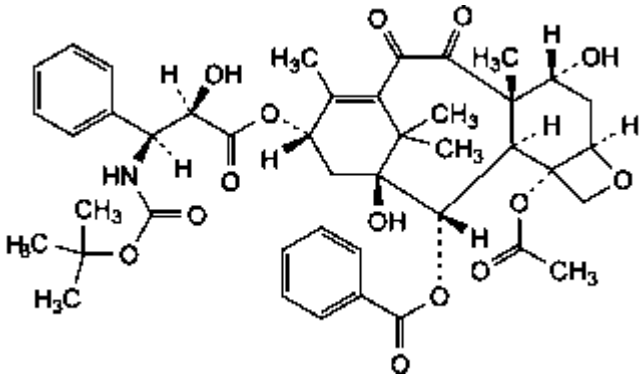
https://thuocngocanh.com/



B. 5β,20-epoxy-1,7β-dihydroxy-9,10-dioxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] (10-deoxy-10-oxodocetaxel),



C. 5β,20-epoxy-1,7α,10β-trihydroxy-9-oxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] (7-*epi*-docetaxel),



D. 5β,20-epoxy-1,7α-dihydroxy-9,10-dioxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] (10-deoxy-10-oxo-7-*epi*-docetaxel).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Docusate Capsules

General Notices

Action and use

Stimulant laxative; faecal softener.

DEFINITION

Docusate Capsules contain a solution of Docusate Sodium in a suitable water miscible vehicle.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of docusate sodium, $C_{20}H_{37}NaO_7S$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve, by heating on a water bath, a capsule in sufficient *water* to produce a solution containing 1% w/v of docusate sodium. Pass 1 mL of this solution with the aid of vacuum through a solid-phase extraction column of 1 mL capacity and containing 0.1 g of an octadecyl-bonded silica sorbent (a Sep-pak C18 column is suitable) previously washed with 2 mL of *methanol*, followed by 5 mL of *water*. Wash the column with 2 mL of *water*, discarding the aqueous eluate and then elute the docusate sodium with 4 mL of *methanol*, retaining the methanol solution.
(2) 0.25% w/v of *docusate sodium BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel (Merck silica gel 60 plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 20 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and expose to iodine vapour.

MOBILE PHASE

2 volumes of 13.5M *ammonia*, 20 volumes of *ethanol (96%)*, 40 volumes of *water* and 50 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuvienthuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 200 mL of *water* to a number of whole capsules containing 1 g of Docusate Sodium and warm on a water bath until the capsules have dissolved. Add 200 mL of *acetonitrile R1*, shake the mixture thoroughly and cool. Add sufficient of a mixture of equal volumes of *acetonitrile R1* and *water* to produce 1000 mL, mix well and filter to obtain a clear solution (Whatman No. 1 paper followed by a 0.4-µm filter is suitable).

(2) 0.1% w/v of *docusate sodium BPCRS* in a mixture of equal volumes of *acetonitrile R1* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Ultracarb ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 214 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

30 volumes of 0.005M *tetrabutylammonium dihydrogen orthophosphate* and 70 volumes of *acetonitrile R1*.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{37}NaO_7S$ in the capsules from the chromatograms obtained using the declared content of $C_{20}H_{37}NaO_7S$ in *docusate sodium BPCRS*.

STORAGE

Docusate Capsules should be kept in an airtight container.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Docusate Oral Solution

General Notices

Action and use

Stimulant laxative; faecal softener.

DEFINITION

Docusate Oral Solution contains 1.0% w/v of Docusate Sodium in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of docusate sodium, $C_{20}H_{37}NaO_7S$

0.95 to 1.05% w/v.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Pass a volume of the oral solution containing 10 mg of docusate sodium, with the aid of vacuum, through a solid phase extraction column of 1 mL capacity and containing 0.1 g of an octadecyl-bonded silica sorbent (a Sep-pak C18 column is suitable) which has been previously washed with 2 mL of *methanol*, followed by 5 mL of *water*. Wash the column with 2 mL of *water*, discarding the aqueous eluate and then elute the docusate sodium with 4 mL of *methanol*, retaining the methanol solution.

(2) 0.25% w/v of *docusate sodium BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose to iodine vapour and examine in daylight.

MOBILE PHASE

2 volumes of 13.5M *ammonia*, 20 volumes of *ethanol (96%)*, 40 volumes of *water* and 50 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuvienthuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Pass a weighed quantity of the oral solution containing 10 mg of docusate sodium, with the aid of vacuum, through a solid-phase extraction column of 1 mL capacity and containing 0.1 g of an octadecyl-bonded silica sorbent (a Sep-pak C18 column is suitable) previously washed with 2 mL of *methanol*, followed by 5 mL of *water*. Wash the column with 2 mL of *water*, discarding the aqueous eluate. Elute the docusate sodium with 4 mL of *methanol* and dilute to 20 mL with a mixture of 70 volumes of *acetonitrile* and 30 volumes of *water*.
(2) 0.05% w/v of *docusate sodium BPCRS* in a mixture of 70 volumes of *acetonitrile* and 30 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with silica gel with a chemically bonded, strongly basic quaternary ammonium anion-exchange coating (10 µm) (Spherisorb SAX is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 214 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1.6 volumes of *orthophosphoric acid*, 350 *v*olumes of *water* and 650 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2) the *symmetry factor* of the peak corresponding to docusate sodium is less than 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{20}H_{37}NaO_7S$, weight in volume, using the declared content of $C_{20}H_{37}NaO_7S$ in *docusate sodium BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

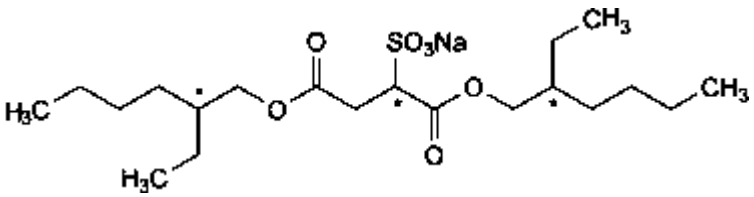
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Docusate Sodium

General Notices

Dioctyl Sodium Sulphosuccinate

(Ph. Eur. monograph 1418)



$C_{20}H_{37}NaO_7S$ 444.6 *577-11-7*

Action and use

Stimulant laxative; faecal softener.

Preparations

Co-danthrusate Capsules

Docusate Capsules

Compound Docusate Enema

Docusate Oral Solution

Paediatric Docusate Oral Solution

Ph Eur

DEFINITION

Sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate.

Content

98.0 to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, waxy masses or flakes, hygroscopic.

Solubility

Sparingly soluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Place about 3 mg of the substance to be examined on a sodium chloride plate, add 0.05 mL of *acetone R* and immediately cover with another sodium chloride plate. Rub the plates together to dissolve the substance to be examined, slide the plates apart and allow the acetone to evaporate.

Comparison *docusate sodium CRS*.

B. In a crucible, ignite 0.75 g in the presence of *dilute sulfuric acid R*, until an almost white residue is obtained. Allow to cool and take up the residue with 5 mL of *water R*. Filter. 2 mL of the filtrate gives reaction (a) of sodium (*2.3.1*).

TESTS

Alkalinity

Dissolve 1.0 g in 100 mL of a mixture of equal volumes of *methanol R* and *water R*, previously neutralised to *methyl red solution R*. Add 0.1 mL of *methyl red solution R*. Not more than 0.2 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator to red.

Related non-ionic substances

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 10 mg of *methyl behenate R* in *hexane R* and dilute to 50 mL with the same solvent.

Test solution (a) Dissolve 0.10 g of the substance to be examined in 2.0 mL of the internal standard solution and dilute to 5.0 mL with *hexane R*. Pass the solution, at a rate of about 1.5 mL/min, through a column 10 mm in internal diameter, packed with 5 g of *basic aluminium oxide R* and previously washed with 25 mL of *hexane R*. Elute with 5 mL of *hexane R* and discard the eluate. Elute with 20 mL of a mixture of equal volumes of *ether R* and *hexane R*. Evaporate the eluate to dryness and dissolve the residue in 2.0 mL of *hexane R*.

Test solution (b) Prepare as described for test solution (a) but dissolving 0.10 g of the substance to be examined in *hexane R*, diluting to 5.0 mL with the same solvent, and using a new column.

Reference solution Dilute 2.0 mL of the internal standard solution to 5.0 mL with *hexane R*.

Column:

— *material*: glass;

— *size*: *l* = 2 m, Ø = 2 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *silanised diatomaceous earth for gas chromatography R* impregnated with 3 per cent *m/m* of *phenyl(50)methyl(50)polysiloxane R*.

Carrier gas *nitrogen for chromatography R*.

Flow rate 30 mL/min.

Temperature:

— *column*: 230 °C;

— *injection port and detector*: 280 °C.

Detection Flame ionisation.

Injection 1 µL.

Run time 2.5 times the retention time of the internal standard.

System suitability There is no peak with the same retention time as the internal standard in the chromatogram obtained with test solution (b).

Limits Test solution (a):

— *any impurity*: for each impurity, not more than the area of the peak due to the internal standard (0.4 per cent).

Chlorides

Maximum 350 ppm.

Dissolve 5.0 g in 50 mL of *ethanol (50 per cent V/V) R*. Titrate with *0.01 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.01 M silver nitrate* is equivalent to 0.3545 mg of Cl.

Sodium sulfate

Maximum 2 per cent.

Dissolve 0.25 g in 40 mL of a mixture of 20 volumes of *water R* and 80 volumes of *2-propanol R*. Adjust the pH to between 2.5 and 4.0 using *perchloric acid solution R*. Add 0.4 mL of *naphtharson solution R* and 0.1 mL of a 0.125 g/L solution of *methylene blue R*. Not more than 1.5 mL of *0.025 M barium perchlorate* is required to change the colour of the indicator from yellowish-green to yellowish-pink.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.250 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

To 1.000 g in a 250 mL conical flask fitted with a reflux condenser add 25.0 mL of *0.5 M alcoholic potassium hydroxide* and heat on a water-bath under reflux for 45 min. Allow to cool. Add 0.25 mL of *phenolphthalein solution R1* and titrate with *0.5 M hydrochloric acid* until the red colour disappears. Carry out a blank titration.

1 mL of *0.5 M alcoholic potassium hydroxide* is equivalent to 0.1112 g of $C_{20}H_{37}NaO_7S$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

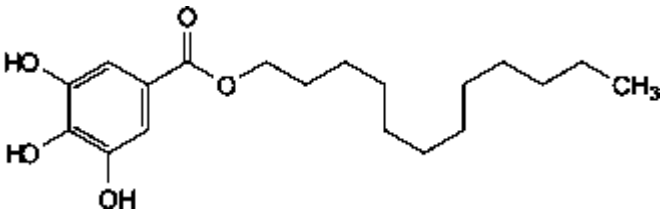
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dodecyl Gallate

General Notices

(Ph. Eur. monograph 2078)



$C_{19}H_{30}O_5$ 338.4 *1166-52-5*

Action and use

Antioxidant.

Ph Eur

DEFINITION

Dodecyl 3,4,5-trihydroxybenzoate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble or practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

A. Determine the melting point (2.2.14) of the substance to be examined. Mix equal parts of the substance to be examined and *dodecyl gallate CRS* and determine the melting point of the mixture. The difference between the melting points (which are about 96 °C) is not greater than 2 °C.

B. Examine the chromatograms obtained in the test for impurity A.

www.webofpharma.com

https://thuocngocanh.com/

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Impurity A

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.20 g of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20 mL with *acetone R*.

Reference solution (a) Dissolve 10 mg of *dodecyl gallate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *gallic acid R* in *acetone R* and dilute to 20 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10 mL with *acetone R*.

Reference solution (d) Dilute 1.0 mL of reference solution (b) to 5 mL with test solution (a).

Plate *TLC silica gel plate R*.

Mobile phase *anhydrous formic acid R*, *ethyl formate R*, *toluene R* (10:40:50 *V/V/V*).

Application 5 µL of test solutions (a) and (b) and reference solutions (a), (c) and (d).

Development Over 2/3 of the plate.

Drying In air for 10 min.

Detection Spray with a mixture of 1 volume of *ferric chloride solution R1* and 9 volumes of *ethanol (96 per cent) R*.

System suitability Reference solution (d):

— the chromatogram shows 2 clearly separated principal spots.

Limit Test solution (a):

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.5 per cent).

Chlorides (2.4.4)

Maximum 100 ppm.

To 1.65 g add 50 mL of *water R*. Shake for 5 min. Filter. 15 mL of the filtrate complies with the test.

Loss on drying (2.2.32)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 70 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in *methanol R* and dilute to 250.0 mL with the same solvent. Dilute 5.0 mL of the solution to 200.0 mL with *methanol R*.

Measure the absorbance (*2.2.25*) at the absorption maximum at 275 nm.

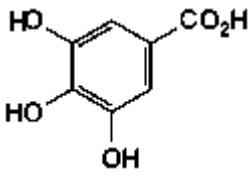
Calculate the content of $C_{19}H_{30}O_5$ taking the specific absorbance to be 321.

STORAGE

In a non-metallic container, protected from light.

IMPURITIES

Specified impurities *A.*



A. 3,4,5-trihydroxybenzoic acid (gallic acid).

Ph Eur

© Crown Copyright 2022

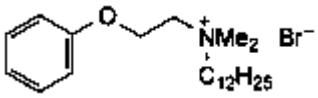
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Domiphen Bromide

General Notices



$C_{22}H_{40}BrNO$ 414.5 *538-71-6*

Action and use

Antiseptic.

DEFINITION

Domiphen Bromide consists chiefly of dodecyldimethyl-2-phenoxyethylammonium bromide. It contains not less than 97.0% and not more than 100.5% of $C_{22}H_{40}BrNO$, calculated with reference to the dried substance.

CHARACTERISTICS

Colourless or faintly yellow, crystalline flakes.

Freely soluble in *water* and in *ethanol (96%)*; soluble in *acetone*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of domiphen bromide (*RS 383*).

B. Dissolve 10 mg in 10 mL of *water* and add 0.1 mL of a 0.5% w/v solution of *eosin* and 100 mL of *water*. An intense pink colour is produced.

C. Yields the reactions characteristic of *bromides*, Appendix VI.

TESTS

Acidity or alkalinity

Add 0.5 mL of *bromothymol blue solution R3* to each of 10 mL of *phosphate buffer pH 6.4* (solution A) and 10 mL of *phosphate buffer pH 7.6* (solution B). Dissolve 0.10 g in 10 mL of *carbon dioxide-free water* and add 0.5 mL of *bromothymol blue solution R3*. The resulting solution is not more yellow than solution A and not more blue than solution B.

Clarity and colour of solution

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 1.0 g in 10 mL of *carbon dioxide-free water*. The solution is not more opalescent than *reference suspension II*, Appendix IV A, and not more intensely coloured than *reference solution* Y_7, Appendix IV B, Method I.

Non-quaternary amines

Carry out the Assay described below using a further 25 mL of the original solution and 10 mL of 0.1M *hydrochloric acid* in place of the 0.1M *sodium hydroxide*. The difference between the volume of *0.05M potassium iodate VS* required in this titration and that required in the Assay is not more than 0.5 mL for each g of substance taken.

Loss on drying

When dried to constant weight at 70° at a pressure not exceeding 0.7 kPa, loses not more than 1.0% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Dissolve 2 g in sufficient *water* to produce 100 mL. Transfer 25 mL to a separating funnel and add 25 mL of *chloroform*, 10 mL of 0.1M *sodium hydroxide* and 10 mL of a freshly prepared 5% w/v solution of *potassium iodide*. Shake well, allow to separate and discard the chloroform layer. Wash the aqueous layer with three 10-mL quantities of *chloroform* and discard the chloroform solutions. Add 40 mL of *hydrochloric acid*, allow to cool and titrate with *0.05M potassium iodate VS* until the deep brown colour is discharged. Add 2 mL of *chloroform* and continue the titration, shaking vigorously, until the chloroform layer no longer changes colour. Carry out a blank titration on a mixture of 10 mL of the freshly prepared potassium iodide solution, 20 mL of *water* and 40 mL of *hydrochloric acid*. The difference between the titrations represents the amount of potassium iodate required. Each mL of *0.05M potassium iodate VS* is equivalent to 41.45 mg of $C_{22}H_{40}BrNO$.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

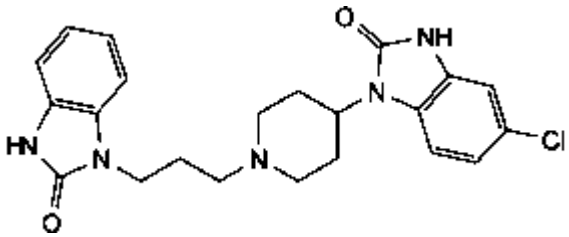
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Domperidone

General Notices

(Ph. Eur. monograph 1009)



$C_{22}H_{24}ClN_5O_2$ 425.9 *57808-66-9*

Action and use

Peripheral dopamine receptor antagonist; antiemetic.

Ph Eur

DEFINITION

5-Chloro-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in dimethylformamide, slightly soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *domperidone CRS*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 0.20 g in dimethylformamide R and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution (a) Dissolve 0.10 g of the substance to be examined in dimethylformamide R and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 20 mL with dimethylformamide R.

Reference solution (a) Dissolve the contents of a vial of domperidone impurity mixture CRS (impurities A and D) in 1 mL of test solution (b).

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with dimethylformamide R. Dilute 1.0 mL of this solution to 10.0 mL with dimethylformamide R.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (3 µm).

Mobile phase:

— *mobile phase A*: 5 g/L solution of ammonium acetate R;

— *mobile phase B*: methanol R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	70 → 0	30 → 100
10 - 12	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with domperidone impurity mixture CRS and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, D + E.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to domperidone (retention time = about 7 min): impurity A = about 0.4; impurities D and E = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to domperidone and impurity D.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 1.4;

— for each impurity, use the concentration of domperidone in reference solution (b).

Limits:

— *sum of impurities D and E*: maximum 0.25 per cent;

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator, until the colour changes from orange-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 42.59 mg of $C_{22}H_{24}ClN_5O_2$.

STORAGE

Protected from light.

IMPURITIES

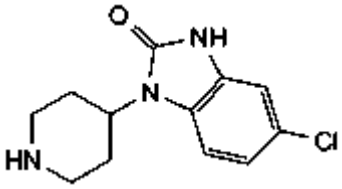
Specified impurities *A, D, E.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

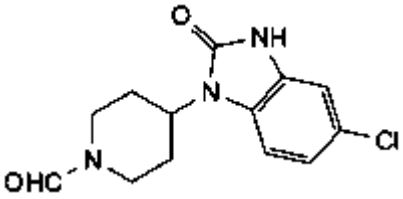
www.webofpharma.com

https://thuocngocanh.com/

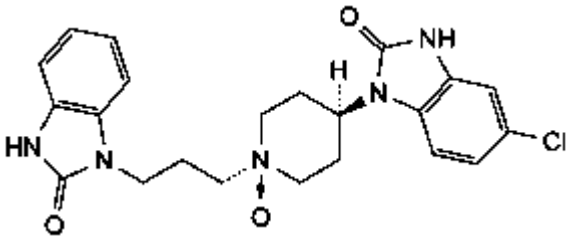
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, F.*



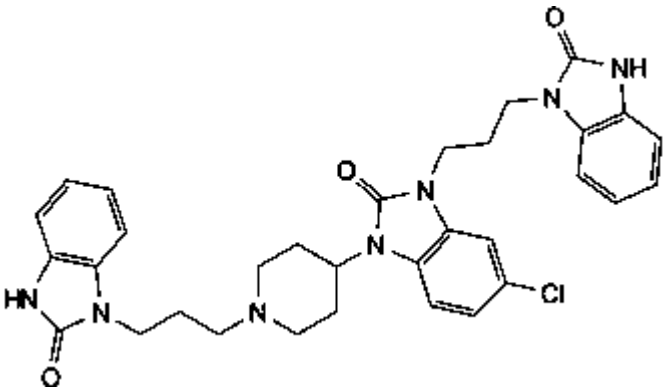
A. 5-chloro-1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one,



B. 4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carbaldehyde,



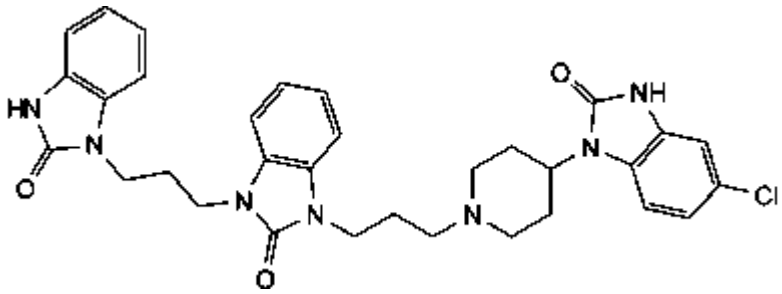
C. (1*s*,4*s*)-4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidine 1-oxide,



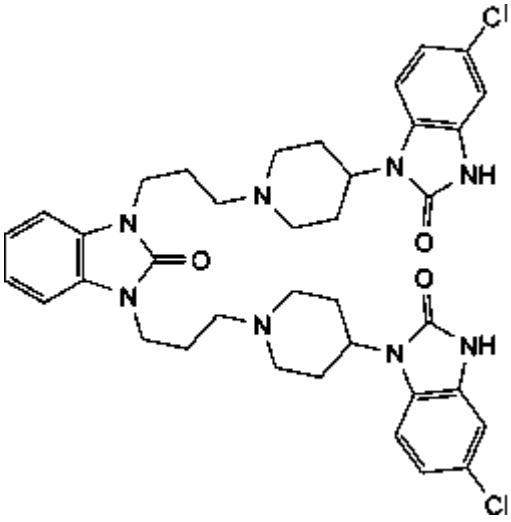
D. 5^6-chloro-1^2,1^3,10^2,10^3-tetrahydro-5^2*H*-1,10(1),5(1,3)-tribenzimidazola-6(4,1)-piperidinadecaphane-1^2,5^2,10^2-trione,

www.webofpharma.com

https://thuocngocanh.com/



E. 1^5-chloro-1^2,1^3,10^2,10^3-tetrahydro-6^2*H*-1,10(1),6(1,3)-tribenzimidazola-2(4,1)-piperidinadecaphane-1^2,6^2,10^2-trione,



F. 1^5,11^5-dichloro-1^2,1^3,11^2,11^3-tetrahydro-6^2*H*-1,11(1),6(1,3)-tribenzimidazola-2(4,1),10(1,4)-dipiperidinaundecaphane-1^2,6^2,11^2-trione.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

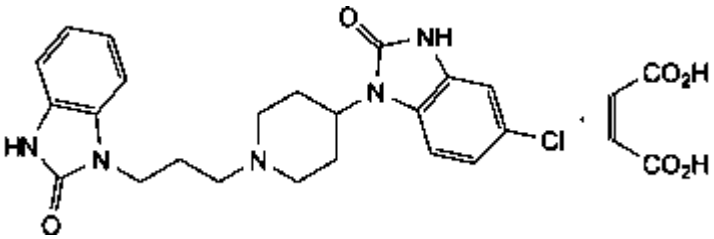
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Domperidone Maleate

General Notices

(Ph. Eur. monograph 1008)



$C_{26}H_{28}ClN_5O_6$ 542.0 *83898-65-1*

Action and use

Peripheral dopamine receptor antagonist; antiemetic.

Preparation

Domperidone Tablets

Ph Eur

DEFINITION

5-Chloro-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one (2*Z*)-but-2-enedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, sparingly soluble in dimethylformamide, slightly soluble in methanol, very slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *domperidone maleate CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *2-propanol R*, evaporate to dryness on a water-bath and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 0.20 g in *dimethylformamide R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution (a) Dissolve 0.10 g of the substance to be examined in *dimethylformamide R* and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 20 mL with *dimethylformamide R*.

Reference solution (a) Dissolve the contents of a vial of *domperidone impurity mixture CRS* (impurity D) in 1 mL of test solution (b).

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *dimethylformamide R*. Dilute 1.0 mL of this solution to 10.0 mL with *dimethylformamide R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 5 g/L solution of *ammonium acetate R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	70 → 0	30 → 100
10 - 12	0	100

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *domperidone impurity mixture CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurities D + E.

Relative retention With reference to domperidone (retention time = about 7 min): maleic acid = about 0.1; impurities D and E = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to domperidone and impurity D.

Calculation of percentage contents:

— for each impurity, use the concentration of domperidone maleate in reference solution (b).

Limits:

— *sum of impurities D and E*: maximum 0.25 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to maleic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Using 0.2 mL of *naphtholbenzein solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from orange-yellow to green.

1 mL of *0.1 M perchloric acid* is equivalent to 54.20 mg of $C_{26}H_{28}ClN_5O_6$.

STORAGE

Protected from light.

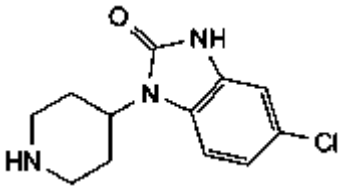
IMPURITIES

www.webofpharma.com

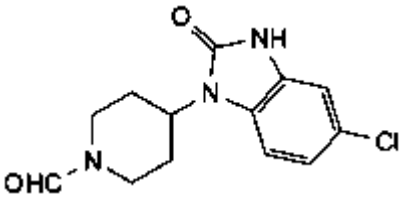
https://thuvienthuocngocanh.com/

Specified impurities D, E.

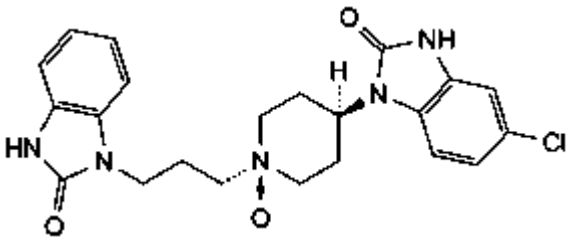
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, F.



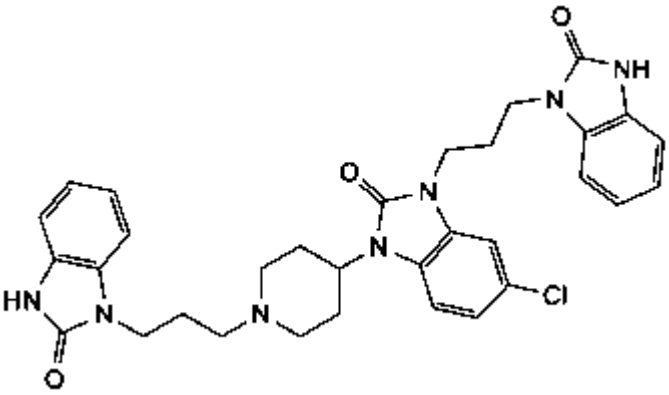
A. 5-chloro-1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one,



B. 4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1-carbaldehyde,



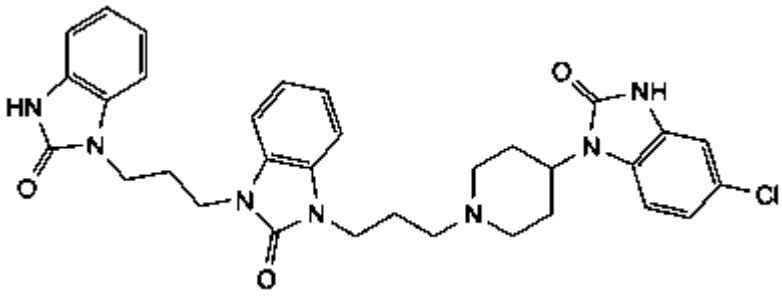
C. (1*s*,4*s*)-4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidine 1-oxide,



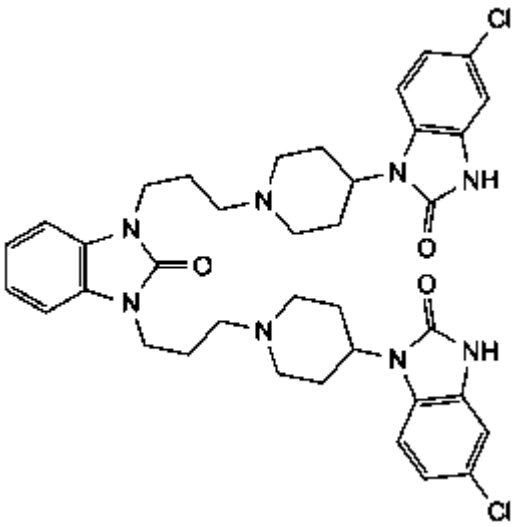
D. 5^6-chloro-1^2,1^3,10^2,10^3-tetrahydro-5^2*H*-1,10(1),5(1,3)-tribenzimidazola-6(4,1)-piperidinadecaphane-1^2,5^2,10^2-trione,

www.webofpharma.com

https://thuocngocanh.com/



E. 1^5-chloro-1^2,1^3,10^2,10^3-tetrahydro-6^2*H*-1,10(1),6(1,3)-tribenzimidazola-2(4,1)-piperidinadecaphane-1^2,6^2,10^2-trione,



F. 1^5,11^5-dichloro-1^2,1^3,11^2,11^3-tetrahydro-6^2*H*-1,11(1),6(1,3)-tribenzimidazola-2(4,1),10(1,4)-dipiperidinaundecaphane-1^2,6^2,11^2-trione.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Domperidone Tablets

General Notices

Action and use

Peripheral dopamine receptor antagonist; antiemetic.

DEFINITION

Domperidone Tablets contain Domperidone Maleate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of domperidone, $C_{22}H_{24}ClN_5O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of equal volumes of *dichloromethane* and *methanol*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 10 mg of domperidone with 10 mL of solvent and filter through a glass microfibre filter (Whatman GF/C is suitable).

(2) 0.127% w/v of *domperidone maleate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a precoated *silica gel F_{254}* plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*. Spray the plate with *potassium iodobismuthate solution* and examine again.

MOBILE PHASE

5 volumes of a solution prepared by dissolving 1.36 g of *sodium acetate* in 50 mL of *water*, adjusting the pH to 4.7 with *dilute acetic acid* and adding sufficient *water* to produce 100 mL, 18 volumes of *methanol*, 23 volumes of *dichloromethane* and 54 volumes of *ethyl acetate*.

CONFIRMATION

Using each method of visualisation, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 20 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 286 nm, Appendix II B using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.001% w/v solution of *domperidone maleate BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of domperidone, $C_{22}H_{24}ClN_5O_2$, in the medium from the absorbances obtained and using the declared content of $C_{22}H_{24}ClN_5O_2$, in *domperidone maleate BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) To a quantity of the powdered tablets containing the equivalent of 50 mg of domperidone add 10 mL of a mixture of equal volumes of 0.01M *hydrochloric acid* and *methanol*, mix with the aid of ultrasound for 20 minutes and filter through a glass microfibre filter (Whatman GF/C is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes with a mixture of equal volumes of 0.01M *hydrochloric acid* and *methanol*. Dilute 1 volume of the resulting solution to 2 volumes with the same solvent.

(3) Dilute 1 volume of solution (2) to 5 volumes of a mixture of equal volumes of 0.01M *hydrochloric acid* and *methanol*.

(4) 0.01% w/v of *domperidone maleate BPCRS* and 0.015% w/v of *droperidol BPCRS* in a mixture of equal volumes of 0.01M *hydrochloric acid* and *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute. Equilibrate the column for at least 30 minutes with *methanol* and equilibrate with the initial mobile phase for at least 5 minutes.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 10 µL of each solution. Inject a mixture of equal volumes of 0.01M *hydrochloric acid* and *methanol* as a blank prior to the solutions.

MOBILE PHASE

Mobile phase A 0.5% w/v solution of *ammonium acetate*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	70→0	30→100	linear gradient
10-12	0	100	isocratic
12-14	0→70	100→30	linear gradient
14-24	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention time of domperidone is about 6.5 minutes and the retention time of droperidol is about 7 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the two principal peaks is at least 2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak in the chromatogram obtained with the blank solution, any peak due to maleic acid near the start of the chromatogram and any peak with an area less than the area of the peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add sufficient *methanol* to 10 whole tablets to produce a solution containing 0.02% w/v of domperidone, mix with the aid of ultrasound for 20 minutes and filter through a glass microfibre filter (Whatman GF/C is suitable). To 50 mL of the filtrate add 1 mL of 0.1M *hydrochloric acid* and sufficient *water* to produce 100 mL.

(2) 0.0127% w/v of *domperidone maleate BPCRS* in a mixture of equal volumes of 0.002M *hydrochloric acid* and *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{24}ClN_5O_2$ in the tablets using the declared content of $C_{22}H_{24}ClN_5O_2$ in *domperidone maleate BPCRS*.

STORAGE

Domperidone Tablets should be stored in an airtight container.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of domperidone.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

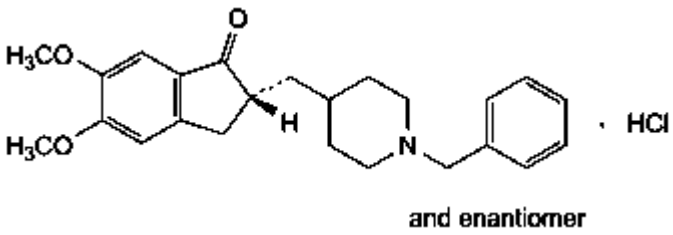
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Donepezil Hydrochloride

General Notices

(Ph. Eur. monograph 2582)



and enantiomer

$C_{24}H_{30}ClNO_3$ 416.0 *120011-70-3*

Action and use

Acetylcholinesterase inhibitor; treatment of dementia in Alzheimer's disease.

Ph Eur

DEFINITION

(2*RS*)-2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, very soluble in methylene chloride, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *donepezil hydrochloride CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Water (see Tests).

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase B, mobile phase A (20:80 *V/V*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 15.0 mg of *donepezil hydrochloride CRS* in the solvent mixture and dilute to 30.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *donepezil for system suitability CRS* (containing impurities C, D and E) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped phenylhexylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: add 15 mL of *triethylamine R* to about 900 mL of *water for chromatography R*, adjust to pH 6.8 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 10	80 → 60	20 → 40
10 - 35	60	40

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 100 µL of test solution (a) and reference solutions (a) and (c).

Identification of impurities Use the chromatogram supplied with *donepezil for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C + E, and impurity D.

Relative retention With reference to donepezil (retention time = about 15 min): impurities C and E = about 0.78; impurity D = about 0.83.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurities C + E, and impurity D in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 30 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— for each impurity, use the concentration of donepezil hydrochloride in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 0.4 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 20 µL of test solution (b) and reference solution (b).

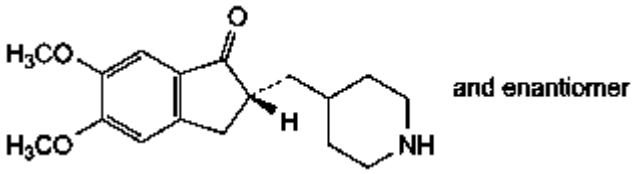
Calculate the percentage content of $C_{24}H_{30}ClNO_3$ taking into account the assigned content of *donepezil hydrochloride CRS*.

IMPURITIES

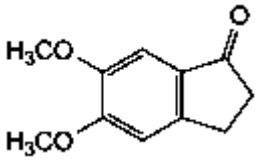
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G.*

www.webofpharma.com

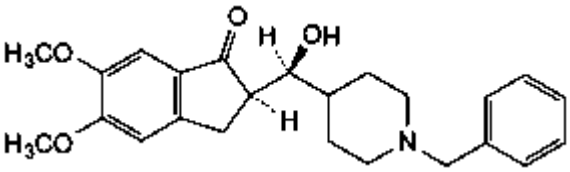
https://thuocngocanh.com/



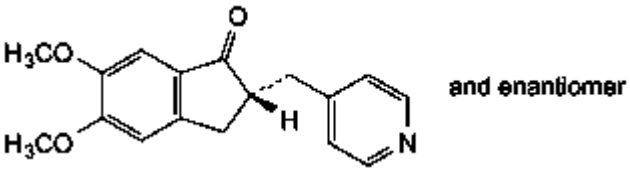
A. (2*RS*)-5,6-dimethoxy-2-[(piperidin-4-yl)methyl]-2,3-dihydro-1*H*-inden-1-one,



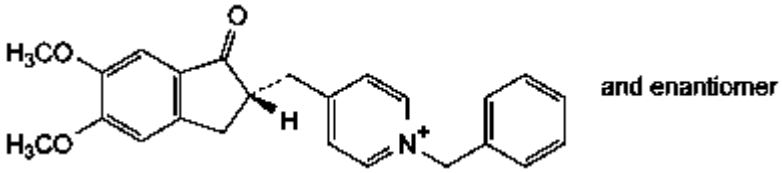
B. 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one,



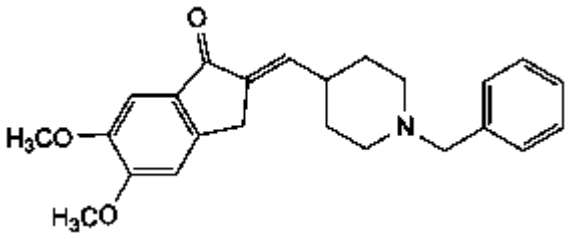
C. (2*R*)-2-[(*S*)-(1-benzylpiperidin-4-yl)(hydroxy)methyl]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one,



D. (2*RS*)-5,6-dimethoxy-2-[(pyridin-4-yl)methyl]-2,3-dihydro-1*H*-inden-1-one,



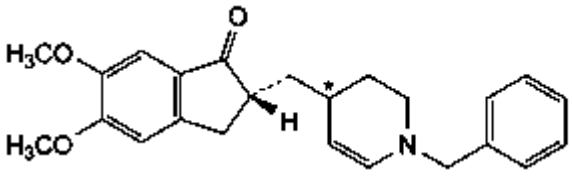
E. 1-benzyl-4-[[(2*RS*)-5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl]methyl]pyridin-1-ium,



F. (2*E*)-2-[(1-benzylpiperidin-4-yl)methylidene]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one,

www.webofpharma.com

https://thuvienthuocngocanh.com/



and enantiomer

G. (2*RS*)-2-[(1-benzyl-1,2,3,4-tetrahydropyridin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

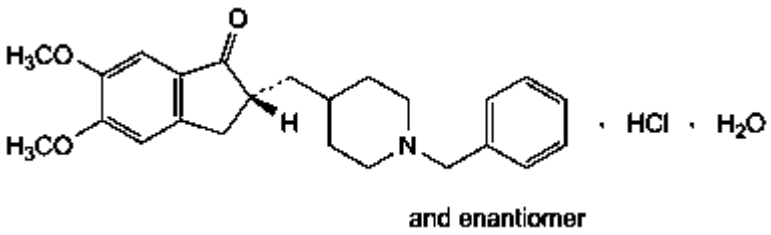
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Donepezil Hydrochloride Monohydrate

General Notices

(Ph Eur. monograph 3067)



and enantiomer

$C_{24}H_{30}ClNO_3,H_2O$ 434.0 *884740-09-4*

Action and use

Acetylcholinesterase inhibitor; treatment of dementia in Alzheimer's disease.

Ph Eur

DEFINITION

(2*RS*)-2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one hydrochloride monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, freely soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *donepezil hydrochloride monohydrate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Water (see Tests).

C. It gives the reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase B, mobile phase A (20:80 *V/V*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 15.0 mg of *donepezil hydrochloride CRS* in the solvent mixture and dilute to 30.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *donepezil for system suitability CRS* (containing impurities C, D and E) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped phenylhexylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: add 15 mL of *triethylamine R* to about 900 mL of *water for chromatography R*, adjust to pH 6.8 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 10	80 → 60	20 → 40
10 - 35	60	40

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 270 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 100 µL of test solution (a) and reference solutions (a) and (c).

Identification of impurities Use the chromatogram supplied with *donepezil for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C + E, and impurity D.

Relative retention With reference to donepezil (retention time = about 15 min): impurities C and E = about 0.78; impurity D = about 0.83.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurities C + E, and impurity D in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 30 for the principal peak in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— for each impurity, use the concentration of donepezil hydrochloride monohydrate in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

4.0 per cent to 6.0 per cent, determined on 0.200 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 20 µL of test solution (b) and reference solution (b).

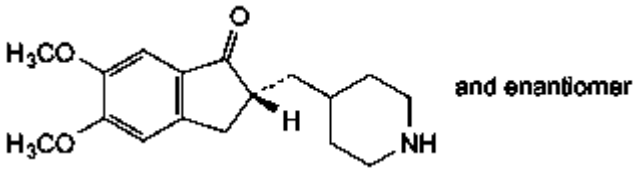
Calculate the percentage content of $C_{24}H_{30}ClNO_3$ taking into account the assigned content of *donepezil hydrochloride CRS*.

IMPURITIES

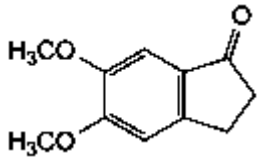
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G.

www.webofpharma.com

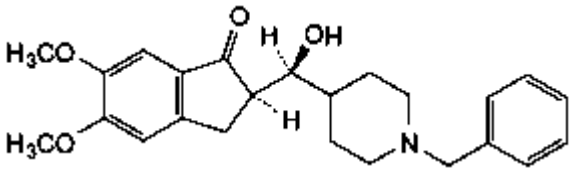
https://thuocngocanh.com/



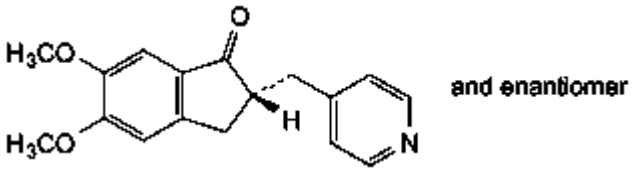
A. (2*RS*)-5,6-dimethoxy-2-[(piperidin-4-yl)methyl]-2,3-dihydro-1*H*-inden-1-one,



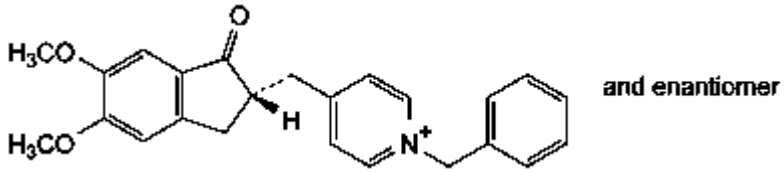
B. 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one,



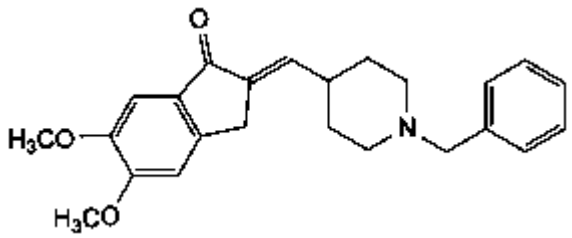
C. (2*R*)-2-[(*S*)-(1-benzylpiperidin-4-yl)(hydroxy)methyl]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one,



D. (2*RS*)-5,6-dimethoxy-2-[(pyridin-4-yl)methyl]-2,3-dihydro-1*H*-inden-1-one,



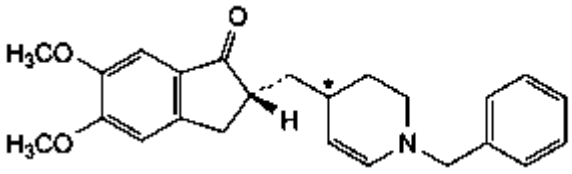
E. 1-benzyl-4-[[(2*RS*)-5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl]methyl]pyridin-1-ium,



F. (2*E*)-2-[(1-benzylpiperidin-4-yl)methylidene]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one,

www.webofpharma.com

https://thuocngocanh.com/



and enantiomer

G. (2*RS*)-2-[(1-benzyl-1,2,3,4-tetrahydropyridin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

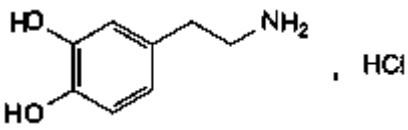
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dopamine Hydrochloride

General Notices

(Ph. Eur. monograph 0664)



$C_8H_{12}ClNO_2$ 189.6 *62-31-7*

Action and use

Dopamine receptor antagonist; beta$_1$-adrenoceptor agonist; alpha-adrenoceptor agonist.

Preparation

Dopamine Infusion

Ph Eur

DEFINITION

4-(2-Aminoethyl)benzene-1,2-diol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent), sparingly soluble in acetone and in methylene chloride.

IDENTIFICATION

First identification: B, E.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, C, D, E.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 40.0 mg in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same acid. Dilute 10.0 mL of this solution to 100.0 mL with *0.1 M hydrochloric acid*.

Spectral range 230-350 nm.

Absorption maximum At 280 nm.

Specific absorbance at the absorption maximum 136 to 150.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dopamine hydrochloride CRS*.

C. Dissolve about 5 mg in a mixture of 5 mL of *1 M hydrochloric acid* and 5 mL of *water R*. Add 0.1 mL of *sodium nitrite solution R* containing 100 g/L of *ammonium molybdate R*. A yellow colour develops which becomes red on the addition of *strong sodium hydroxide solution R*.

D. Dissolve about 2 mg in 2 mL of *water R* and add 0.2 mL of *ferric chloride solution R2*. A green colour develops which changes to bluish-violet on the addition of 0.1 g of *hexamethylenetetramine R*.

E. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_6 or Y_6 (2.2.2, *Method II*).

Dissolve 0.4 g in *water R* and dilute to 10 mL with the same solvent.

Acidity or alkalinity

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Add 0.1 mL of *methyl red solution R* and 0.75 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 1.5 mL of *0.01 M hydrochloric acid*. The solution is red.

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light.*

Buffer solution Dissolve 21 g of *citric acid monohydrate R* in 200 mL of *1 M sodium hydroxide* and dilute to 1000 mL with *water R*. To 600 mL of this solution add 400 mL of *0.1 M hydrochloric acid*.

Test solution Dissolve 50 mg of the substance to be examined in mobile phase A and dilute to 25 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 10 mg of *3-O-methyldopamine hydrochloride R* (impurity B) and 10 mg of *4-O-methyldopamine hydrochloride R* (impurity A) in mobile phase A and dilute to 100 mL with mobile phase A. Dilute 6 mL of this solution to 25 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase:

— *mobile phase A*: dissolve 1.08 g of *sodium octanesulfonate R* in 880 mL of the buffer solution and add 50 mL of *methanol R* and 70 mL of *acetonitrile R*;

— *mobile phase B*: dissolve 1.08 g of *sodium octanesulfonate R* in 700 mL of the buffer solution and add 100 mL of *methanol R* and 200 mL of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10
5 - 20	90 → 40	10 → 60
20 - 25	40	60

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Retention time Dopamine = about 5 min.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurities B and A.

Limits:

— *unspecificied impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached.

Dissolve 0.150 g in 10 mL of *anhydrous formic acid R*. Add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

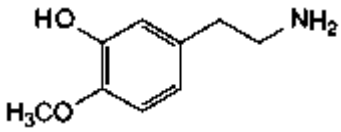
1 mL of *0.1 M perchloric acid* is equivalent to 18.96 mg of $C_8H_{12}ClNO_2$.

STORAGE

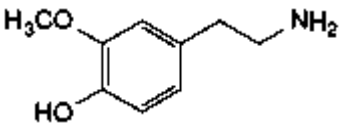
In an airtight container, under nitrogen, protected from light.

IMPURITIES

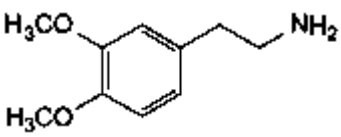
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C.



A. 5-(2-aminoethyl)-2-methoxyphenol (4-*O*-methyldopamine),



B. 4-(2-aminoethyl)-2-methoxyphenol (3-*O*-methyldopamine),



C. 2-(3,4-dimethoxyphenyl)ethanamine.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dopamine Infusion

General Notices

Dopamine Intravenous Infusion

Action and use

Dopamine receptor antagonist; beta$_1$-adrenoceptor agonist; alpha-adrenoceptor agonist.

DEFINITION

Dopamine Infusion is a sterile solution containing Dopamine Hydrochloride. It is supplied as a ready-to-use solution or it is prepared by diluting either Dopamine Sterile Concentrate or Dopamine Hydrochloride for Injection with a suitable diluent in accordance with the manufacturer's instructions.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

When supplied as a ready-to-use solution, the intravenous infusion complies with the following requirements.

Content of dopamine hydrochloride, $C_8H_{11}NO_2,HCl$

95.0 to 105.0% of the stated amount.

Content of glucose, $C_6H_{12}O_6$

4.75 to 5.25% w/v.

CHARACTERISTICS

A colourless liquid.

IDENTIFICATION

A. Saturate a volume containing 0.1 g of Dopamine Hydrochloride with *sodium chloride* and extract with three 20-mL quantities of *butan-1-ol*. Filter the combined extracts through *anhydrous sodium sulfate* and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dopamine hydrochloride *(RS 113)*.

B. To a volume containing 10 mg of Dopamine Hydrochloride add 0.1 mL of *iron(III) chloride solution R1*. An intense green colour is produced.

TESTS

Acidity

www.webofpharma.com

https://thuocngocanh.com/

pH, 3.0 to 4.5, Appendix V L.

5-Hydroxymethylfurfural

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the intravenous infusion.

(2) 0.0025% w/v of *5-hydroxymethylfurfural* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 284 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.05M *disodium hydrogen orthophosphate* adjusted to pH 7.0 with *orthophosphoric acid*.

LIMITS

In the chromatogram obtained with solution (1), the area of any peak corresponding to 5-hydroxymethylfurfural is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.05%, determined with reference to the content of glucose).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the infusion with sufficient mobile phase to produce a solution expected to contain 0.032% w/v of Dopamine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 50 volumes with the mobile phase.

(3) Dilute 1 volume of solution (1) and 1 volume of a solution containing 0.030% w/v each of *4-ethylcatechol* and *3,4-dimethoxyphenethylamine* to 50 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

Under the prescribed conditions, the retention time of dopamine is about 5 minutes, of 4-ethylcatechol about 3 minutes and of 3,4-dimethoxyphenethylamine, about 12 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.25 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%);

www.webofpharma.com

https://thuocngocanh.com/

not more than one such peak has an area greater than the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the intravenous infusion, if necessary, with *water BET* to give a solution containing 1.6 mg of Dopamine Hydrochloride per mL (solution A). The endotoxin limit concentration of solution A is 26.67 IU per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the infusion with mobile phase to produce a solution expected to contain 0.0032% w/v of Dopamine Hydrochloride.
(2) 0.0032% w/v of *dopamine hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of 0.1M *disodium edetate*, 10 volumes of *glacial acetic acid*, 300 volumes of *acetonitrile* and 700 volumes of 0.005M *sodium dodecyl sulfate*.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}NO_2$,HCl in the infusion using the declared content of $C_8H_{11}NO_2$,HCl in *dopamine hydrochloride BPCRS*.

DOPAMINE STERILE CONCENTRATE

DEFINITION

Dopamine Sterile Concentrate is a sterile solution of Dopamine Hydrochloride in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of dopamine hydrochloride, $C_8H_{11}NO_2$,HCl

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

www.webofpharma.com

https://thuocngocanh.com/

A colourless or pale yellow solution.

IDENTIFICATION

A. Extract a volume containing 0.1 g of Dopamine Hydrochloride with 10 mL of *butan-1-ol*. Filter the extract through *anhydrous sodium sulfate* and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dopamine hydrochloride *(RS 113)*.

B. To a volume containing 10 mg of Dopamine Hydrochloride add 0.05 mL of *iron(III) chloride solution R1*. An intense green colour is produced.

TESTS

Acidity

pH, 2.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the concentrate containing 0.15 g of Dopamine Hydrochloride to 5 mL with *methanol*.

(2) 0.0075% w/v of *4*-O-*methyldopamine hydrochloride* in *methanol*.

(3) 0.0075% w/v each of *3*-O-*methyldopamine hydrochloride* and *4*-O-*methyldopamine hydrochloride* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air for 15 minutes and spray evenly and abundantly with a mixture, prepared immediately before use, of equal volumes of *iron(III) chloride solution R1* and *potassium hexacyanoferrate(III) solution*.

MOBILE PHASE

2 volumes of *anhydrous formic acid*, 7 volumes of *water*, 36 volumes of *methanol* and 52 volumes of *chloroform*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

Any *secondary spot* with an Rf value higher than that of the principal spot in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.25%).

Bacterial endotoxins

www.webofpharma.com

https://thuocngocanh.com/

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the sterile concentrate with *water BET* to give a solution containing 1.6 mg of Dopamine Hydrochloride per mL (solution A). The endotoxin limit concentration of solution A is 26.67 IU per mL.

ASSAY

Carry out the method described in the requirements for the ready-to-use solution.

STORAGE

Dopamine Sterile Concentrate should be protected from light.

DOPAMINE HYDROCHLORIDE FOR INJECTION

DEFINITION

Dopamine Hydrochloride for Injection is a sterile material consisting of Dopamine Hydrochloride with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of dopamine hydrochloride, $C_8H_{11}NO_2,HCl$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A white or almost white, crystalline powder.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of dopamine hydrochloride *(RS 113)*.

B. Dissolve 10 mg of the substance being examined in 2 mL of *water* and add 0.05 mL of *iron(III) chloride solution R1*. An intense green colour is produced.

TESTS

Acidity

pH of a 4% w/v solution in a 1.0% w/v solution of *sodium metabisulfite*, 2.5 to 5.5, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Dissolve a quantity of the contents of the sealed container to produce a solution containing 3.0% w/v of Dopamine Hydrochloride.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.0075% w/v of *4-O-methyldopamine hydrochloride*.

(3) 0.0075% w/v each of *3-O-methyldopamine hydrochloride* and *4-O-methyldopamine hydrochloride*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air for 15 minutes and spray evenly and abundantly with a mixture, prepared immediately before use, of equal volumes of *iron(III) chloride solution R1* and *potassium hexacyanoferrate(III) solution*.

MOBILE PHASE

2 volumes of *anhydrous formic acid,* 7 volumes of *water*, 36 volumes of *methanol* and 52 volumes of *chloroform*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

Any *secondary spot* with an Rf value higher than that of the principal spot in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.25%).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing 1.6 mg of Dopamine Hydrochloride per mL (solution A). The endotoxin limit concentration of solution A is 26.67 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve sufficient of the mixed contents of the 10 containers in the mobile phase to produce a solution containing 0.0032% w/v of Dopamine Hydrochloride.

(2) 0.0032% w/v of *dopamine hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under the Assay for the ready-to-use solution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{11}NO_2$,HCl in a container of average content weight using the declared content of $C_8H_{11}NO_2$,HCl in *dopamine hydrochloride BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

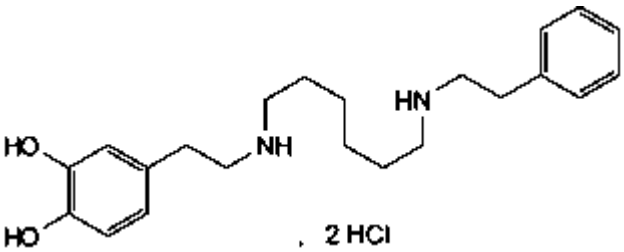
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dopexamine Hydrochloride

General Notices

(Dopexamine Dihydrochloride, Ph. Eur. monograph 1748)



$C_{22}H_{34}Cl_2N_2O_2$ 429.4 *86484-91-5*

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

Ph Eur

DEFINITION

4-[2-[[6-[(2-Phenylethyl)amino]hexyl]amino]ethyl]benzene1,2-diol dihydrochloride.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, sparingly soluble in ethanol (96 per cent) and in methanol, practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *dopexamine dihydrochloride CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, Method II).

Dissolve 0.10 g in 0.1 M hydrochloric acid and dilute to 10 mL with the same acid.

pH (2.2.3)

3.7 to 5.7.

Dissolve 0.20 g in carbon dioxide-free water R and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of dopexamine impurity B CRS in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of dopexamine impurity F CRS in mobile phase A and dilute to 100 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: mix 5 volumes of buffer solution pH 2.5 R and 95 volumes of water R;

— *mobile phase B*: mix 5 volumes of buffer solution pH 2.5 R and 95 volumes of a 60 per cent *V/V* solution of acetonitrile R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	81 → 77	19 → 23

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
10 - 25	77 → 50	23 → 50
25 - 30	50	50

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Preconditioning of the column Rinse for 5 min with a mixture of 19 volumes of mobile phase B and 81 volumes of mobile phase A.

Injection 20 µL.

Relative retention With reference to dopexamine (retention time = about 5 min): impurity A = about 0.5; impurity B = about 2.0; impurity C = about 2.3; impurity D = about 2.8; impurity E = about 2.9; impurity F = about 3.0; impurity I = about 3.6; impurity J = about 5.0; impurity K = about 5.9.

System suitability Reference solution (b):

— *resolution*: minimum 2 between the peaks due to dopexamine and impurity B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.4; impurity F = 0.7;

— *impurities A, B, C, D, E, F, I, K*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurity J

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Detection Spectrophotometer at 210 nm.

Limit:

— *impurity J*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Water (*2.5.12*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 10 IU/mg.

ASSAY

Carry out the titration immediately after preparation of the test solution [In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.]

Dissolve 0.150 g in 10 mL of *anhydrous formic acid R*. Add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 21.47 mg of $C_{22}H_{34}Cl_2N_2O_2$.

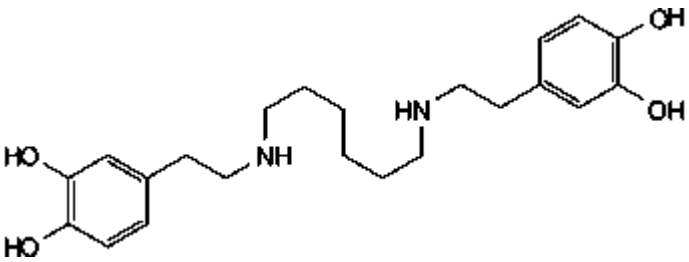
STORAGE

Protected from light.

IMPURITIES

Specified impurities A, B, C, D, E, F, I, J, K.

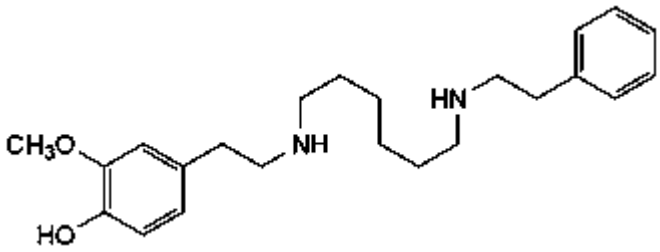
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) G, H.



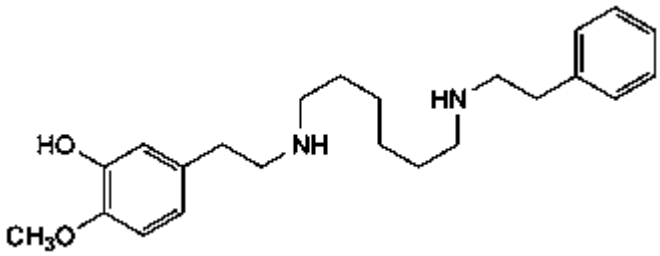
A. 4,4′-[hexane-1,6-diylbis(iminoethylene)]dibenzene-1,2-diol,

www.webofpharma.com

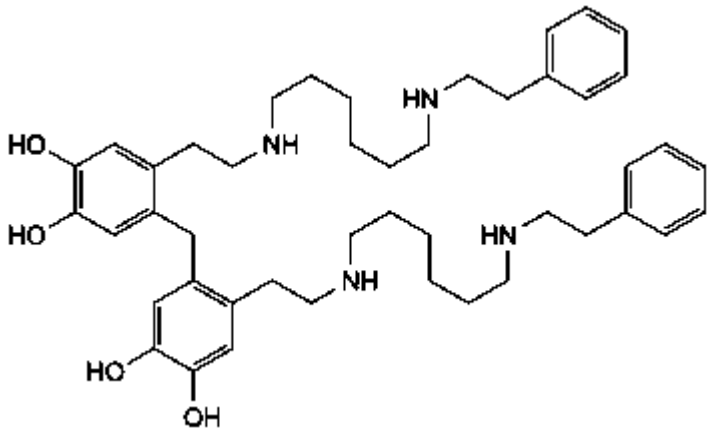
https://thuocngocanh.com/



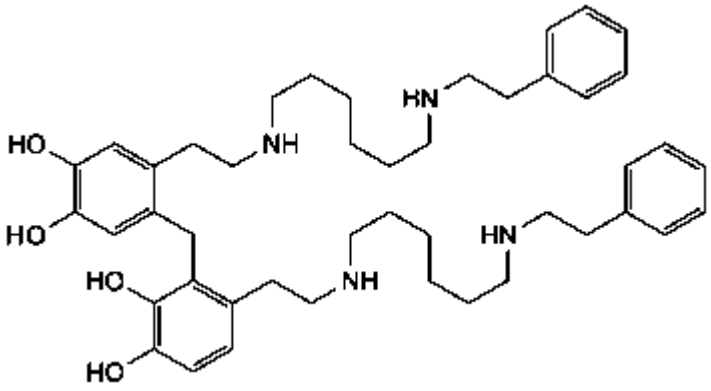
B. 2-methoxy-4-[2-[[6-[(2-phenylethyl)amino]hexyl]amino]ethyl]phenol,



C. 2-methoxy-5-[2-[[6-[(2-phenylethyl)amino]hexyl]amino]ethyl]phenol,



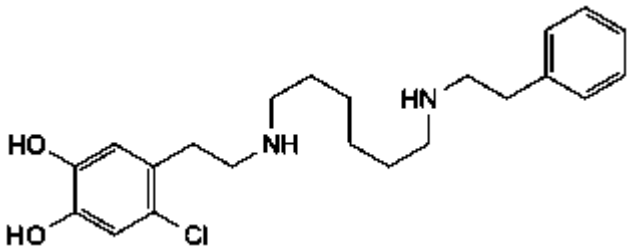
D. 4,4′-methylenebis[5-[2-[[6-[(2-phenylethyl)amino]hexyl]amino]ethyl]benzene-1,2-diol],



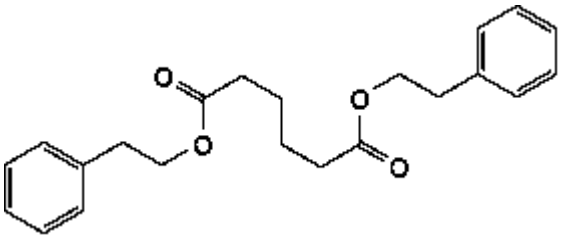
E. 3-[4,5-dihydroxy-2-[2-[[6-[(2-phenylethyl)amino]hexyl]amino]ethyl]benzyl]-4-[2-[[6-[(2-phenylethyl)amino]hexyl]amino]ethyl]benzene-1,2-diol,

www.webofpharma.com

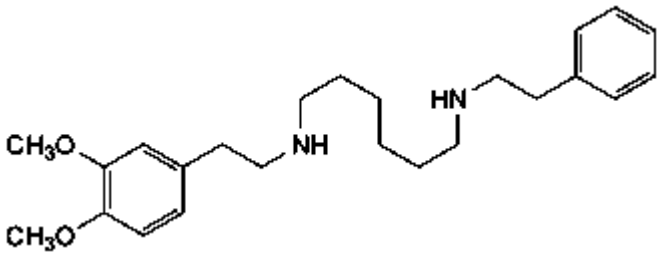
https://thuocngocanh.com/



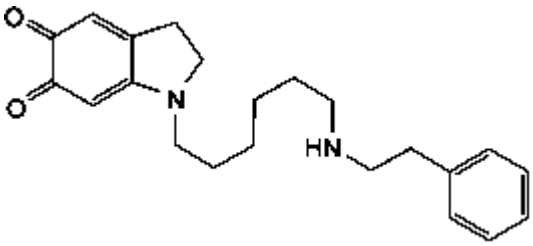
F. 4-chloro-5-[2-[[6-[(2-phenylethyl)amino]hexyl]amino]ethyl]benzene-1,2-diol,



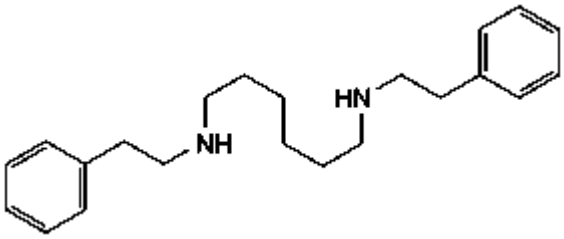
G. bis(2-phenylethyl) hexanedioate,



H. *N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*′-(2-phenylethyl)hexane-1,6-diamine,



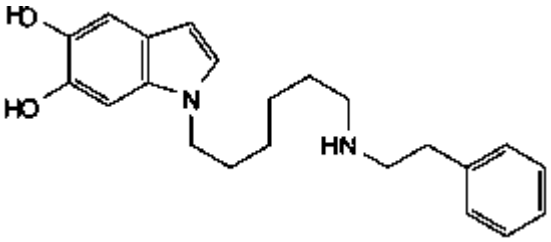
I. 1-[6-[(2-phenylethyl)amino]hexyl]-2,3-dihydro-1*H*-indole5,6-dione (dopexamine aminochrome),



J. *N*,*N*′-bis(2-phenylethyl)hexane-1,6-diamine,

www.webofpharma.com

https://thuvienthuocngocanh.com/



K. 1-[6-[(2-phenylethyl)amino]hexyl]-1*H*-indole-5,6-diol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dorzolamide and Timolol Eye Drops

General Notices

Action and use

Carbonic anhydrase inhibitor + beta-adrenoceptor antagonist; treatment of glaucoma and ocular hypertension.

DEFINITION

Dorzolamide and Timolol Eye Drops are a sterile solution of Dorzolamide Hydrochloride and Timolol Maleate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of dorzolamide, $C_{10}H_{16}N_2O_4S_3$

95.0 to 105.0% of the stated amount.

Content of timolol, $C_{13}H_{24}N_4O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Dilute a quantity of the eye drops to produce a solution containing the equivalent of 0.5% w/v of dorzolamide.

(2) 0.15% w/v of *timolol maleate BPCRS*.

(3) 0.5% w/v of *dorzolamide hydrochloride BPCRS*.

(4) 0.5% w/v of *dorzolamide hydrochloride BPCRS* and 0.15% w/v of *timolol maleate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *concentrated ammonia*, 20 volumes of *methanol* and 80 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

CONFIRMATION

In the chromatogram obtained with solution (1) the spot with the lower Rf value corresponds to the principal spot in the chromatogram obtained with solution (2) and the spot with the higher Rf value corresponds to the principal spot in the chromatogram obtained with solution (3).

B. In the Assay for dorzolamide, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. In the Assay for timolol, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 5.0 to 6.0, Appendix V L.

Related substances

For dorzolamide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *acetonitrile* and 19 volumes of a 0.2% v/v solution of *orthophosphoric acid*.

(1) Use the eye drops diluted to contain the equivalent of 0.01% w/v of dorzolamide.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dilute 1 volume of solution (2) to 5 volumes.

(4) 0.011% w/v of *dorzolamide hydrochloride BPCRS* and 0.000011% w/v each of *dorzolamide impurity B BPCRS* and *dorzolamide impurity D BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx-C8 and Zorbax SB-C8 are suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 253 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A *Acetonitrile*.

Mobile phase B 0.2% v/v *orthophosphoric acid*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 15.0	5	95	isocratic
15.0 - 15.1	5 → 95	95 → 5	linear gradient
15.1 - 20.0	95	5	isocratic
20.0 - 20.1	95 → 5	5 → 95	linear gradient
20.1 - 30.0	5	95	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to dorzolamide (retention time = about 12 minutes) are: impurity D = about 0.8; impurity B = about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution factor* between the peaks due to dorzolamide and impurity B is at least 3.0;

the *resolution factor* between the peaks due to impurity D and dorzolamide is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 1.1 times the area of the principal peak in the chromatogram obtained with solution (2) (1.1%);

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 1.3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.3%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

For timolol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) Use the eye drops diluted to contain the equivalent of 0.025% w/v of timolol.

(2) Dilute 1 volume of volume (1) to 200 volumes. Dilute 2 volumes of this solution to 5 volumes.

www.webofpharma.com

https://thuvienthuocngocanh.com/

(3) Add 8 mL of 0.1M *sodium hydroxide* to 90 mg of *timolol maleate BPCRS*, heat at 70° for 15 hours, cool and add sufficient mobile phase to produce 50 mL. Mix 1 volume of this solution with 4 volumes of a 0.140% w/v solution of *dorzolamide hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-2 and Symmetry C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 295 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of timolol.

MOBILE PHASE

2 volumes of *methanol* and 3 volumes of a 1.1% w/v solution of *sodium dihydrogen orthophosphate monohydrate* adjusted to pH 2.8 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to timolol (retention time = about 5.7 minutes) are: dorzolamide = about 0.5; impurity G = about 0.6, impurity B = about 0.7; impurity D = about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to impurity G and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B, D or G is not greater than twice the area of the principal peak obtained with solution (2) (0.4% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

For dorzolamide

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *acetonitrile* and 19 volumes of 0.2% v/v solution of *orthophosphoric acid*.

(1) Use the eye drops diluted to contain the equivalent of 0.01% w/v of dorzolamide.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.011% w/v of *dorzolamide hydrochloride BPCRS*.

(3) 0.011% w/v of *dorzolamide hydrochloride BPCRS* and 0.000011% w/v each of *dorzolamide impurity B BPCRS* and *dorzolamide impurity D BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances for dorzolamide may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to dorzolamide and impurity B is at least 3.0;

the *resolution factor* between the peaks due to impurity D and dorzolamide is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{16}N_2O_4S_3$ in the eye drops using the declared content of $C_{10}H_{16}N_2O_4S_3$,HCl in *dorzolamide hydrochloride BPCRS*. Each mg of $C_{10}H_{16}N_2O_4S_3$,HCl is equivalent to 0.8990 mg of $C_{10}H_{16}N_2O_4S_3$.

For timolol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) Use the eye drops diluted to contain the equivalent of 0.025% w/v of timolol.

(2) 0.0342% w/v of *timolol maleate BPCRS*.

(3) Add 8 mL of 0.1M *sodium hydroxide* to 90 mg of *timolol maleate BPCRS*, heat at 70° for 15 hours, cool and add sufficient mobile phase to produce 50 mL. Mix 1 volume of this solution with 4 volumes of a 0.140% w/v solution of *dorzolamide hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances for timolol may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to timolol impurity G and timolol impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{24}N_4O_3S$, in the eye drops using the declared content of $C_{13}H_{24}N_4O_3S,C_4H_4O_4$ in *timolol maleate BPCRS*. Each mg of $C_{13}H_{24}N_4O_3S,C_4H_4O_4$ is equivalent to 0.7316 mg of $C_{13}H_{24}N_4O_3S$.

LABELLING

The quantity of Dorzolamide Hydrochloride is stated in terms of the equivalent amount of dorzolamide and the quantity of Timolol Maleate is stated in terms of the equivalent amount of timolol.

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B and D listed under Dorzolamide Hydrochloride and impurities B, D and G listed under Timolol Maleate.

© Crown Copyright 2022

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dorzolamide Eye Drops

General Notices

Action and use

Carbonic anhydrase inhibitor; treatment of glaucoma and ocular hypertension.

DEFINITION

Dorzolamide Eye Drops are a sterile solution of Dorzolamide Hydrochloride in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of dorzolamide, $C_{10}H_{16}N_2O_4S_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions in *methanol*.

(1) Dilute a quantity of the eye drops to produce a solution containing the equivalent of 0.5% w/v of dorzolamide.

(2) 0.5% w/v of *dorzolamide hydrochloride BPCRS*.

(3) 0.5% w/v of *dorzolamide hydrochloride BPCRS* and 0.15% w/v of *timolol maleate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *concentrated ammonia*, 20 volumes of *methanol* and 80 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 5.0 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Use the eye drops diluted to contain the equivalent of 0.01% w/v of dorzolamide.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) Dilute 1 volume of solution (2) to 5 volumes.
(4) 0.011% w/v of *dorzolamide hydrochloride BPCRS* and 0.000011% w/v each of *dorzolamide impurity B BPCRS* and *dorzolamide impurity D BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx-C8 and Zorbax SB-C8 are suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 253 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of dorzolamide.

MOBILE PHASE

1 volume of *acetonitrile* and 19 volumes of a 0.2% v/v solution of *orthophosphoric acid*, previously adjusted to pH 3.0 using *triethylamine*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to dorzolamide (retention time = about 11 minutes) are: impurity D = about 0.9; impurity B = about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution factor* between the peaks due to dorzolamide and impurity B is at least 3.0;

the *resolution factor* between the peaks due to impurity D and dorzolamide is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity B is not greater than 1.3 times the area of the principal peak obtained with solution (2) (1.3%);

the area of any peak corresponding to impurity D is not greater than the area of the principal peak obtained with solution (3) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak obtained with solution (3) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 1.5 times the area of the principal peak obtained with solution (2) (1.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Use the eye drops diluted to contain the equivalent of 0.01% w/v of dorzolamide.

(2) 0.011% w/v of *dorzolamide hydrochloride BPCRS*.

(3) 0.011% w/v of *dorzolamide hydrochloride BPCRS* and 0.000011% w/v each of *dorzolamide impurity B BPCRS* and *dorzolamide impurity D BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to dorzolamide and impurity B is at least 3.0;

the *resolution factor* between the peaks due to impurity D and dorzolamide is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{16}N_2O_4S_3$ in the eye drops using the declared content of $C_{10}H_{16}N_2O_4S_3$,HCl in *dorzolamide hydrochloride BPCRS*. Each mg of $C_{10}H_{16}N_2O_4S_3$,HCl is equivalent to 0.8990 mg of $C_{10}H_{16}N_2O_4S_3$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of dorzolamide.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B and D listed under Dorzolamide Hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

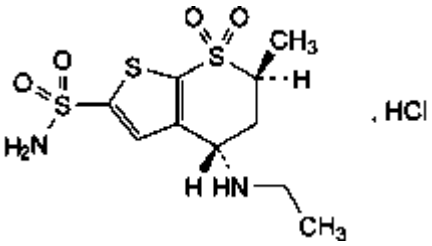
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dorzolamide Hydrochloride

General Notices

(Ph. Eur. monograph 2359)



$C_{10}H_{17}ClN_2O_4S_3$ 360.9 *130693-82-2*

Action and use

Carbonic anhydrase inhibitor; treatment of glaucoma and ocular hypertension.

Preparations

Dorzolamide Eye Drops

Dorzolamide and Timolol Eye Drops

Ph Eur

DEFINITION

(4*S*,6*S*)-4-(Ethylamino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, slightly soluble in methanol, very slightly soluble in anhydrous ethanol.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *dorzolamide hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. It complies with the test for impurity A (see Tests).

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Impurity A

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *glacial acetic acid R*, *1,1-dimethylethyl methyl ether R* (3:10:87 *V/V/V*).

Test solution In a centrifuge tube, dissolve 20.0 mg of the substance to be examined in 4 mL of *dilute ammonia R4*, add 4 mL of *ethyl acetate R*, and mix. Separate the organic layer and transfer it to a separate centrifuge tube. Add 4 mL of *ethyl acetate R* to the aqueous layer, mix, separate the organic layer, and combine it with the 1st extract. Evaporate the combined organic layers to dryness in a water-bath at 50 °C under a stream of *nitrogen R*. Dissolve the residue in 3 mL of *acetonitrile R*, add 0.06 mL of *(S)-(-)-α-methylbenzyl isocyanate R*, and heat in a water-bath at 50 °C for 5 min. Evaporate to dryness in a water-bath at 50 °C under a stream of *nitrogen R*. Dissolve the residue in 10 mL of the solvent mixture.

Reference solution In a centrifuge tube, dissolve 18.0 mg of *dorzolamide hydrochloride CRS* and 2.0 mg of *dorzolamide impurity A CRS* in 4 mL of *dilute ammonia R4*, and proceed as indicated for the test solution beginning with “add 4 mL of *ethyl acetate R*, and mix”.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm).

Mobile phase *water R*, *acetonitrile R*, *heptane R*, *1,1-dimethylethyl methyl ether R* (0.2:2:35:63 *V/V/V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 3 times the retention time of dorzolamide.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to dorzolamide (retention time = about 10 min): impurity A = about 1.4.

System suitability Reference solution:

— *resolution*: minimum 4.0 between the peaks due to dorzolamide and impurity A.

Calculate the percentage content of impurity A using the following expression:

$$\frac{A}{A+B} \times 100$$

A	=	area of the peak due to impurity A in the chromatogram obtained with the test solution;
B	=	area of the peak due to dorzolamide in the chromatogram obtained with the test solution.

Limit:

— *impurity A*: maximum 0.5 per cent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 30.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 2 mg of *dorzolamide for system suitability CRS* (containing impurity C) in 2 mL of mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 65 mL of *acetonitrile R* and 935 mL of a 3.7 g/L solution of *potassium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 30	100 → 50	0 → 50

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
30 - 37	50 → 100	50 → 0
37 - 44	100	0

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *dorzolamide for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to dorzolamide (retention time = about 11 min): impurity C = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity C and dorzolamide.

Limits:

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*, using sonication if necessary.

Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 1st and the 3rd points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.05 mg of $C_{10}H_{17}N_2O_4S_3Cl$.

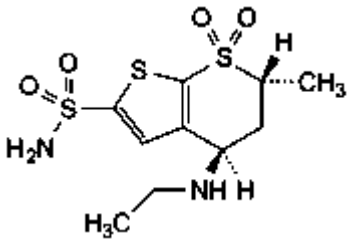
www.webofpharma.com

https://thuocngocanh.com/

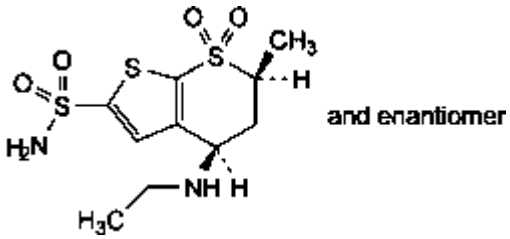
IMPURITIES

Specified impurities A, C.

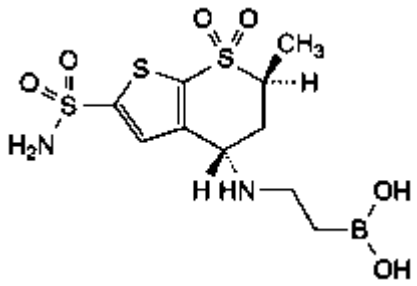
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, D.



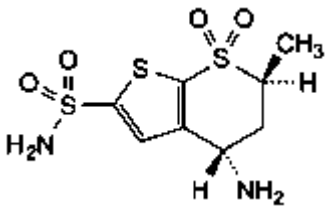
A. (4*R*,6*R*)-4-(ethylamino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide,



B. (4*RS*,6*SR*)-4-(ethylamino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide,



C. [2-[[(4*S*,6*S*)-6-methyl-7,7-dioxo-2-sulfamoyl-4,5,6,7-tetrahydro-7λ^6-thieno[2,3-*b*]thiopyran-4-yl]amino]ethyl]boronic acid,



D. (4*S*,6*S*)-4-amino-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dosulepin Capsules

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Dosulepin Capsules contain Dosulepin Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of dosulepin hydrochloride, $C_{19}H_{21}NS,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Extract a quantity of the contents of the capsules containing 0.1 g of Dosulepin Hydrochloride with 20 ml of *absolute ethanol*, filter and remove the ethanol from the filtrate by evaporation. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dosulepin hydrochloride *(RS 114)*.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the contents of the capsules containing 0.25 g of Dosulepin Hydrochloride by shaking for 2 minutes with 5 ml of *chloroform*, centrifuge and use the supernatant liquid.

(2) Dilute 2 ml of solution (1) to 5 ml with *chloroform*.

(3) 0.010% w/v each of *3-(dibenzo*[b,e]*thiepin-11(6*H*)-ylidene)*-N,N-*dimethylaminopropan-1-amine* S*-oxide hydrochloride BPCRS* and *dibenzo*[b,e]*thiepin-11(6*H*)-one BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel 60 F_{254} precoated plate* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µl of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

www.webofpharma.com

https://thietbiuocngocanh.com/

MOBILE PHASE

1 volume of 13.5M *ammonia*, 10 volumes of *propan-2-ol* and 90 volumes of *1,2-dichloroethane*.

LIMITS

The spot with the lower Rf value in the chromatogram obtained with solution (3) is more intense than any corresponding spot in the chromatogram obtained with solution (2) (0.5%).

In the chromatogram obtained with solution (1), any *secondary spot* other than any spot corresponding to the spot with the lower Rf value in the chromatogram obtained with solution (3) is not more intense than the proximate spot in the chromatogram obtained with solution (3) (0.2%).

Z-Isomer

Carry out the method for *gas chromatography*, Appendix III B.

(1) Extract a quantity of the mixed contents of 20 capsules containing 25 mg of Dosulepin Hydrochloride with 5 ml of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.50% w/v of *dosulepin hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.8 m × 3 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 3% w/w of cyanopropylmethyl phenyl methyl silicone fluid (OV-225 is suitable).

(b) Use *helium* as the carrier gas at 1.7 ml per minute.

(c) Use isothermal conditions maintained at 200°.

(d) Use an inlet temperature of 200°.

(e) Use a flame ionisation detector at a temperature of 200°.

(f) Inject 1 µl of each solution.

LIMITS

In the chromatogram obtained with solution (2), a peak due to *Z*-dosulepin is present with a retention time of approximately 0.83 relative to the retention time of the principal peak which is due to *E*-dosulepin.

In the chromatogram obtained with solution (1), the area of any peak corresponding to *Z*-dosulepin is not greater than 7.5% of the sum of the areas of the peaks due to *Z*-dosulepin and *E*-dosulepin.

ASSAY

Extract a quantity of the mixed contents of 20 capsules containing 0.5 g of Dosulepin Hydrochloride with 20 ml followed by four 10 ml quantities of *chloroform*, filtering each extract through the same filter. Evaporate the combined extracts to dryness, dissolve the residue in 100 ml of *acetone*, add 10 ml of *mercury(II) acetate solution* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 3 ml of a saturated solution of *methyl orange* in *acetone* as indicator. Each ml of *0.1M perchloric acid VS* is equivalent to 33.19 mg of $C_{19}H_{21}NS,HCl$.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

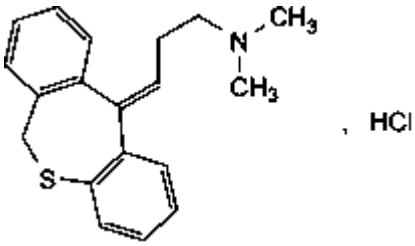
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dosulepin Hydrochloride

General Notices

(Ph. Eur. monograph 1314)



$C_{19}H_{22}ClNS$ 331.9 *897-15-4*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparations

Dosulepin Capsules

Dosulepin Oral Solution

Dosulepin Tablets

Ph Eur

DEFINITION

(*E*)-3-(Dibenzo[*b*,*e*]thiepin-11(6*H*)-ylidene)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or faintly yellow, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 25.0 mg in a 1 g/L solution of *hydrochloric acid R* in *methanol R* and dilute to 100.0 mL with the same solution. Dilute 2.0 mL to 50.0 mL with a 1 g/L solution of *hydrochloric acid R* in *methanol R*.

Spectral range 220-350 nm.

Absorption maxima 231 nm and 306 nm.

Shoulder About 260 nm.

Specific absorbance at the absorption maximum at 231 nm 660 to 730.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *dosulepin hydrochloride CRS*.

C. Dissolve about 1 mg in 5 mL of *sulfuric acid R*. A dark red colour is produced.

D. Dissolve 19 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

Dissolve 1 g in *water R* and dilute to 20 mL with the same solvent.

pH (2.2.3)

4.2 to 5.2.

Dissolve 1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 12.5 mg of *dosulepin impurity A CRS* in 5 mL of *methanol R* and dilute to 50.0 mL with the mobile phase. Dilute 0.5 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *dosulepin for system suitability CRS* (containing impurity E) in 5 mL of *methanol R* and dilute to 20 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped cyanosilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase 0.83 per cent *V/V* solution of *perchloric acid R*, *propanol R*, *methanol R1*, *water for chromatography R* (1:10:30:60 *V/V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 5 µL.

Run time 2.5 times the retention time of dosulepin.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *dosulepin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity E.

Relative retention With reference to dosulepin (retention time = about 14 min): impurity A = about 0.3; impurity E = about 0.92.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to dosulepin.

Limits:

— *impurity E*: not more than 5 per cent of the sum of the areas of the peak due to impurity E and the principal peak in the chromatogram obtained with the test solution (5 per cent);

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than E*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5 mL of *anhydrous acetic acid R* and 35 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 33.19 mg of $C_{19}H_{22}ClNS$.

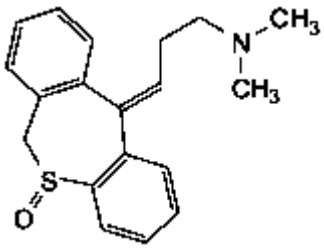
STORAGE

Protected from light.

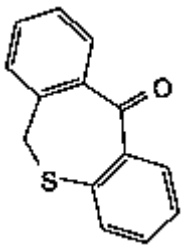
IMPURITIES

Specified impurities A, E.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D.



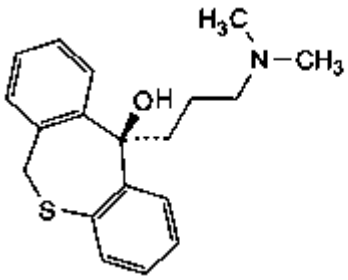
A. (*E*)-11-[3-(dimethylamino)propylidene]-6,11-dihydro-5*H*-5λ^4-dibenzo[*b*,*e*]thiepin-5-one,



www.webofpharma.com

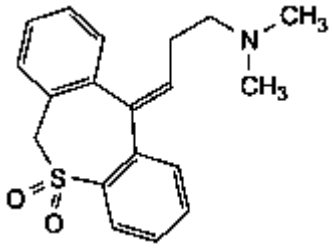
https://thuocngocanh.com/

B. dibenzo[*b*,*e*]thiepin-11(6*H*)-one,

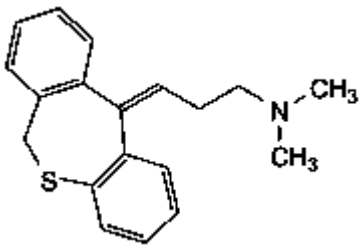


and enantiomer

C. (11*RS*)-11-[3-(dimethylamino)propyl]-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol,



D. (*E*)-11-[3-(dimethylamino)propylidene]-6,11-dihydro-5*H*-5λ^6-dibenzo[*b*,*e*]thiepin-5,5-dione,



E. (*Z*)-3-(dibenzo[*b*,*e*]thiepin-11(*6H*)-ylidene)-*N*,*N*-dimethylpropan-1-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dosulepin Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Dosulepin Oral Solution is a solution of Dosulepin Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of dosulepin hydrochloride, $C_{19}H_{21}NS,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 2 mL of 10M *sodium hydroxide* to a quantity of the oral solution containing 25 mg of Dosulepin Hydrochloride and extract with three 5-mL quantities of *dichloromethane*. Combine the dichloromethane extracts, evaporate to dryness and dissolve the residue in sufficient *dichloromethane* to produce 5 mL.

(2) 0.5% w/v of *dosulepin hydrochloride BPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel 60 F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 10 volumes of *propan-2-ol* and 90 volumes of *1,2-dichloroethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://nhathuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.5 to 5.5, Appendix V L.

Impurity A and *Z*-isomer

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the oral solution with the mobile phase, shake well and add sufficient mobile phase to produce a solution containing 0.05% w/v of Dosulepin Hydrochloride.

(2) Dissolve 12.5 mg of [*3-(dibenzo[b,e]thiepin-11(6*H*)-ylidene*-N,N-*dimethylaminopropan-1-amine* S-*oxide hydrochloride BPCRS* (impurity A) in 5 mL of *methanol*, add sufficient mobile phase to produce 50 mL and dilute 3 volumes of the resulting solution to 100 volumes with the mobile phase.

(3) Dilute 1 volume of a 0.5% w/v solution of *dosulepin hydrochloride BPCRS* in *methanol* to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *nitrile silica gel for chromatography* (5 µm) (Genesis CN, Luna CN and Microsorb CN are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 229 nm.

(f) Inject 5 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 2.5 times the retention time of dosulepin.

MOBILE PHASE

1 volume of 0.83% v/v *perchloric acid*, 10 volumes of *propanol*, 30 volumes of *methanol* and 60 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time of dosulepin (*E*-isomer) is about 25 minutes and the relative retention of *Z*-dosulepin to *E*-dosulepin is about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 4.0 where H_p is the height above the baseline of the peak due to *Z*-dosulepin and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to *E*-dosulepin.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to *Z*-dosulepin is not greater than 5% of the sum of the areas of the principal peak (*E*-dosulepin) and the peak due to Z-dosulepin in the chromatogram obtained with solution (3) (5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a weighed quantity of the oral solution containing 50 mg of Dosulepin Hydrochloride in the mobile phase, add sufficient mobile phase to produce 200 mL, mix thoroughly and filter through a 0.45-µm nylon filter.
(2) 0.025% w/v of *dosulepin hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (22 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (RP-18 Spheri-10 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

15 volumes of 0.04M *sodium dihydrogen orthophosphate*, which has been adjusted to pH 5.6 with *triethylamine*, 20 volumes of *acetonitrile* and 65 volumes of *methanol*.

SYSTEM SUITABILITY

The Assay is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is not less than 2.0 and not more than 3.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{19}H_{21}NS$,HCl, weight in volume, using the declared content of $C_{19}H_{21}NS$,HCl in *dosulepin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of the monograph include impurities A and E listed under Dosulepin Hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dosulepin Tablets

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Dosulepin Tablets contain Dosulepin Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dosulepin hydrochloride, $C_{19}H_{21}NS$, HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Remove the coating. Shake a quantity of the powdered tablet cores containing 0.2 g of Dosulepin Hydrochloride with 20 mL of *dichloromethane*, centrifuge, filter the supernatant liquid and evaporate the filtrate to dryness. Dissolve the residue in the minimum quantity of *ethanol (70%)* and add an excess of *ether*. Filter the precipitate, wash with *ether* and dry at 60° at a pressure of 2 kPa for 5 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dosulepin hydrochloride *(RS 114)*. Examine the substance as a dispersion in *liquid paraffin*.

TESTS

Related substances

Carry out the method for *thin layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.25 g of Dosulepin Hydrochloride for 2 minutes with 5 mL of *dichloromethane*, centrifuge and use the supernatant liquid.

(2) Dilute 2 mL of solution (1) to 5 mL with *dichloromethane*.

(3) 0.01% w/v each of *dosulepin impurity A EPCRS* and *dibenzo[b,e]thiepin-11(6H)-one BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck F254 plates are suitable).

(b) Use the mobile phase described below.

(c) Apply 5 µL of each solution.

(d) After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

1 volume of 13.5M *ammonia*, 10 volumes of *propan-2-ol* and 90 volumes of *1,2-dichloroethane*.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the spot with the lower Rf value is more intense than any corresponding spot in the chromatogram obtained with solution (2).

LIMITS

In the chromatogram obtained with solution (1), any secondary spot other than any spot corresponding to the spot with the lower Rf value in the chromatogram obtained with solution (3), is not more intense than the proximate spot in the chromatogram obtained with solution (3) (0.2%).

Z-Isomer

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 25 mg of Dosulepin Hydrochloride with 5 mL of *methanol* for 15 minutes, centrifuge and use the supernatant liquid.
(2) 0.50% w/v of *dosulepin hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.8 m × 3 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 3% w/w of *cyanopropylmethyl phenyl methyl silicone fluid* (OV-225 is suitable).
(b) Use a column temperature of 200°.
(c) Use injection temperature of 230°.
(d) Inject 1 µL of each solution.
(e) Use *nitrogen* as a carrier gas.

When the chromatogram is recorded under the prescribed conditions the retention time of the peak due to *Z*-dosulepin relative to *E*-dosulepin is approximately 0.8.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to *Z*-dosulepin is not greater than 7.5% of the sum of the areas of the peaks due to *Z*-dosulepin and *E*-dosulepin.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Dosulepin Hydrochloride with 60 mL of 0.1M *hydrochloric acid* for 30 minutes, dilute to 100 mL with 0.1M *hydrochloric acid* and filter. Discard the first 25 mL of the filtrate. Dilute 25 mL of the remaining filtrate to 100 mL with 0.1M *hydrochloric acid*.
(2) 0.0125% w/v of *dosulepin hydrochloride BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuvienthuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 231 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

10 volumes of *tetrahydrofuran*, 40 volumes of *acetonitrile* and 50 volumes of a 0.5% w/v solution of *potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{21}NS,HCl$ using the declared content of $C_{19}H_{21}NS,HCl$ in *dosulepin hydrochloride BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

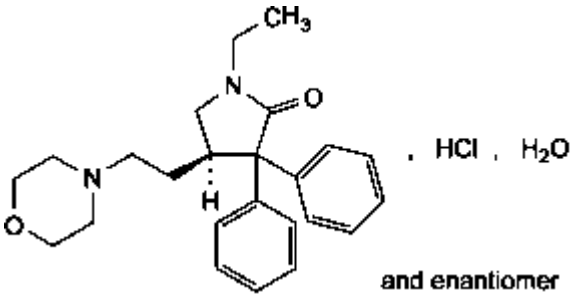
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxapram Hydrochloride

General Notices

(Ph. Eur. monograph 1201)



$C_{24}H_{31}ClN_2O_2,H_2O$ 433.0 *7081-53-0*

Action and use

Respiratory stimulant.

Preparation

Doxapram Injection

Ph Eur

DEFINITION

(4*RS*)-1-Ethyl-4-[2-(morpholin-4-yl)ethyl]-3,3-diphenylpyrrolidin-2-one hydrochloride monohydrate.

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *doxapram hydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *doxapram hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase Solution of *ammonia R* containing 17 g/L of NH_3, *2-propanol R*, *2-methylpropanol R* (10:10:80 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *dilute potassium iodobismuthate solution R* and examine immediately.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.000 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dilute 10 mL of solution S to 25 mL with *water R*.

pH (2.2.3)

3.5 to 5.0.

Dilute 5 mL of solution S to 25 mL with *carbon dioxide-free water R*.

www.webofpharma.com

https://thuocngocanh.com/

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 5.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *doxapram impurity B CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase. To 1.0 mL of the solution, add 1.0 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 50 volumes of *acetonitrile R* and 50 volumes of a 0.82 g/L solution of *sodium acetate R* adjusted to pH 4.5 with *glacial acetic acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Run time 4 times the retention time of doxapram.

Retention time Doxapram = about 6 min.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to doxapram and impurity B.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

3.0 per cent to 4.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

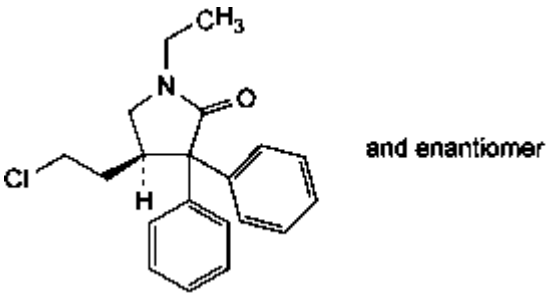
Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 10 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*) using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

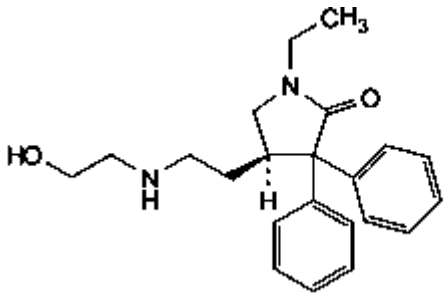
1 mL of *0.1 M sodium hydroxide* is equivalent to 41.50 mg of $C_{24}H_{31}ClN_2O_2$.

IMPURITIES



and enantiomer

A. (4*RS*)-4-(2-chloroethyl)-1-ethyl-3,3-diphenylpyrrolidin-2-one,



and enantiomer

B. (4*RS*)-1-ethyl-4-[2-[(2-hydroxyethyl)amino]ethyl]-3,3-diphenylpyrrolidin-2-one.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxapram Injection

General Notices

Action and use

Respiratory stimulant.

DEFINITION

Doxapram Injection is a sterile solution of Doxapram Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of doxapram hydrochloride, $C_{24}H_{30}N_2O_2,HCl,H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. To a volume containing 50 mg of Doxapram Hydrochloride add 10 mL of *water* and 2 mL of 1M *sodium hydroxide* and extract with two 10 mL quantities of *ether*. Wash the combined extracts with 5 mL of *water*, dry over *anhydrous sodium sulfate*, filter and evaporate to dryness. Recrystallise the residue from 10 mL of 0.01M *methanolic hydrochloric acid*. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of doxapram hydrochloride *(RS 116)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution obtained in the Assay exhibits maxima at 253, 258 and 265 nm.

C. Yields the reactions characteristic *of chlorides*, Appendix VI.

TESTS

Acidity

pH of a solution containing 1% w/v of doxapram hydrochloride, 3.5 to 5.0, Appendix V L.

ASSAY

Dilute a volume containing 0.2 g of Doxapram Hydrochloride to 250 mL with *water*. Measure the *absorbance* of the resulting solution at the maximum at 258 nm, Appendix II B. Calculate the content of $C_{24}H_{30}N_2O_2,HCl,H_2O$ in the injection from the *absorbance* of a 0.08% w/v solution of *doxapram hydrochloride BPCRS* using the declared content of $C_{24}H_{30}N_2O_2,HCl,H_2O$ in *doxapram hydrochloride BPCRS*.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Doxapram Injection should not be allowed to freeze.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

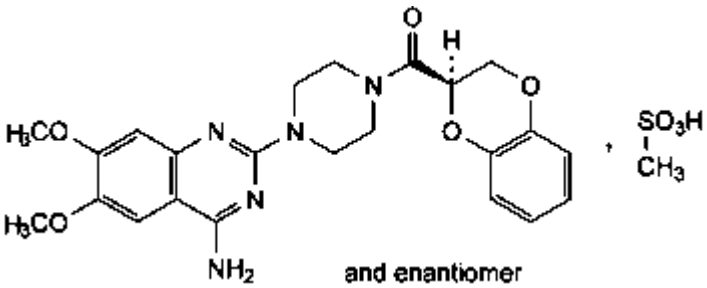
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxazosin Mesilate

General Notices

(Ph. Eur. monograph 2125)



$C_{24}H_{29}N_5O_8S$ 547.6 *77883-43-3*

Action and use

Alpha$_1$-adrenoceptor antagonist.

Ph Eur

DEFINITION

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl][(2*RS*)-2,3-dihydro-1,4-benzodioxin-2-yl]methanone methanesulfonate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in doxazosin mesilate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods *2.5.37. Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, *2.5.38. Methyl, ethyl and isopropyl methanesulfonate in active substances* and *2.5.39. Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

White or almost white, crystalline powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Slightly soluble in water, soluble in a mixture of 15 volumes of water and 35 volumes of tetrahydrofuran, slightly soluble in methanol, practically insoluble in acetone.

It shows polymorphism (5.9); some forms may be hygroscopic.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *doxazosin mesilate CRS*.

If the spectra obtained in the solid state show differences, mix 1 part of the substance to be examined and 1 part of the reference substance separately with 10 parts of *anhydrous ethanol R* and heat to boiling. Continue heating the suspension under a reflux condenser for about 3 h. Cool and filter. Record new spectra using the previously dried residues on the filters.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, *Method II*).

Dissolve 1.0 g in a mixture of 15 mL of *water R* and 35 mL of *tetrahydrofuran R*.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in 5 mL of mobile phase B, adding *water R*, and dilute to 50.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 25.0 mg of *doxazosin mesilate CRS* in 5 mL of mobile phase B, adding *water R*, and dilute to 50.0 mL with *water R*.

Reference solution (c) Dissolve 5 mg of *doxazosin impurity D CRS* and 5 mg of *doxazosin impurity F CRS* in 5 mL of mobile phase B, adding *water R*, and dilute to 50 mL with *water R*. Dilute 1 mL of this solution to 5 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: 1.5 g/L solution of *phosphoric acid R*;

— *mobile phase B*: 1.5 g/L solution of *phosphoric acid R* in *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10
5 - 40	90 → 50	10 → 50
40 - 45	50	50

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and F.

Relative retention With reference to doxazosin (retention time = about 30 min): impurity D = about 0.5; impurity F = about 0.6.

System suitability Reference solution (c):

— *resolution*: minimum 4.5 between the peaks due to impurities D and F.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 1.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

www.webofpharma.com

https://thuocngocanh.com/

Injection Test solution and reference solution (b).

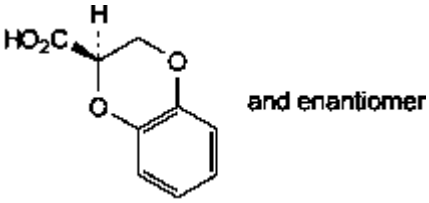
Calculate the percentage content of $C_{24}H_{29}N_5O_8S$ taking into account the assigned content of *doxazosin mesilate CRS*.

STORAGE

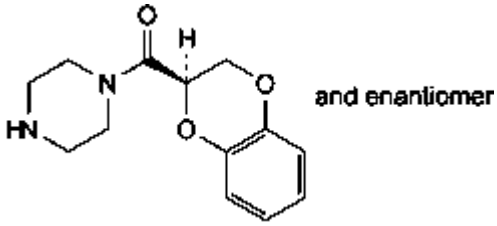
In an airtight container.

IMPURITIES

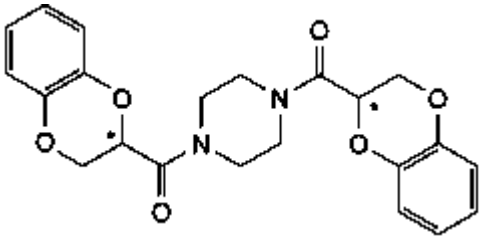
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H.*



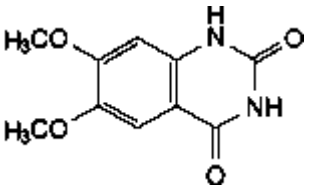
A. (2*RS*)-2,3-dihydro-1,4-benzodioxine-2-carboxylic acid,



B. [(2*RS*)-2,3-dihydro-1,4-benzodioxin-2-yl](piperazin-1-yl)methanone,



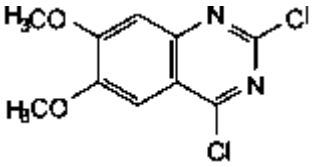
C. (piperazine-1,4-diyl)bis[[(2Ξ)-2,3-dihydro-1,4-benzodioxin-2-yl]methanone],



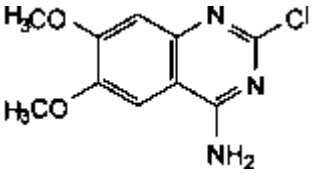
D. 6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione,

www.webofpharma.com

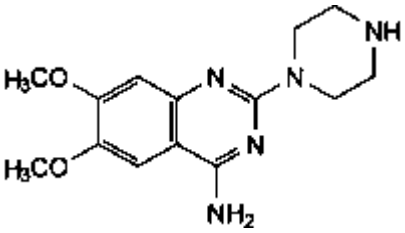
https://thuvienthuocngocanh.com/



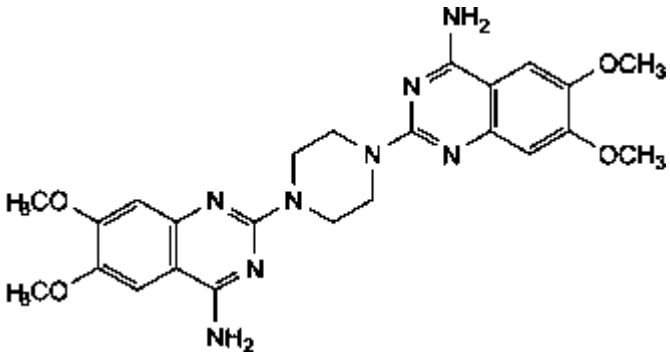
E. 2,4-dichloro-6,7-dimethoxyquinazoline,



F. 2-chloro-6,7-dimethoxyquinazolin-4-amine,



G. 6,7-dimethoxy-2-(piperazin-1-yl)quinazolin-4-amine,



H. 2,2′-(piperazine-1,4-diyl)bis(6,7-dimethoxyquinazolin-4-amine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxepin Capsules

General Notices

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

DEFINITION

Doxepin Capsules contain Doxepin Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of doxepin, $C_{19}H_{21}NO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Wash a quantity of the contents of the capsules containing the equivalent of 100 mg of doxepin with three 5-mL quantities of *petroleum spirit (boiling range, 40° to 60°)*. Dry in air, extract the residue with three 10-mL quantities of *chloroform*, evaporate the combined extracts to dryness and dry the residue at 105°. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of doxepin hydrochloride *(RS 117)*.

B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Z-Isomer

13.0 to 18.5%, when determined by the following method.

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) Extract a quantity of the mixed contents of 20 capsules containing the equivalent of 25 mg of doxepin with 5 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.5% w/v of *doxepin hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a film (3 µm) of 6% cyanopropylphenyl siloxane and 94% polydimethylsiloxane (DB-624 is suitable).

(b) Use *helium* as the carrier gas at 20 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

(c) Use an oven temperature maintained at 200°.

(d) Use an inlet temperature of 240°.

(e) Use a flame ionisation detector maintained at a temperature of 300°.

(f) Use a split ratio of 1:10.

(g) Inject 1 µL of each solution.

When the chromatograms are recorded under the prescribed conditions the retention of *E*-doxepin is about 29 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), a peak due to *Z*-doxepin immediately precedes the principal peak due to *E*-doxepin and the *resolution* between the peaks due to *Z*-doxepin and *E*-doxepin is at least 2.0.

DETERMINATION OF CONTENT

Measure the areas or heights of the peaks due to the *Z*- and *E*-isomers in the chromatograms obtained with solutions (1) and (2) and calculate the content of *Z*-isomer in the substance being examined using the declared content of *Z*-isomer in *doxepin hydrochloride BPCRS*.

Related substances (other than the *Z*-Isomer)

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A. Prepare the solutions immediately before use and protect them from light.

Solvent A A mixture of 2 volumes of 2M *sodium hydroxide* and 1000 volumes of mobile phase.

(1) Dissolve with the aid of ultrasound a quantity of the contents of the capsules containing the equivalent of 100 mg of doxepin in 100 mL of solvent A and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A and further dilute 1 volume to 10 volumes with solvent A.

(3) Dissolve the contents of a vial of *doxepin impurity standard BPCRS* in 25 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna C18 (2) is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

20 volumes of *acetonitrile R1*, 30 volumes of 0.01M *disodium hydrogen orthophosphate*, adjusted to pH 7.7 using 0.02M *orthophosphoric acid*, and 50 volumes of *methanol*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity A and impurity C is at least 1.5;

the *resolution* between the peaks due to impurity C and impurity B is at least 1.5.

LIMITS

Identify any peak corresponding to impurity B using the chromatogram obtained with solution (3) and multiply the area of the peak by a correction factor of 1.7.

In the chromatogram obtained with solution (1):

identify any peaks corresponding to impurity A, B and C using the chromatogram obtained with solution (3) and the chromatogram supplied with *doxepin impurity standard BPCRS*;

the *Z*-isomer may appear as a shoulder on the peak due to Doxepin, the requirement for the symmetry factor in the range of 0.8-1.5 does not apply to this peak;

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any peak corresponding to impurity C is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other peak is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of all the peaks is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A, as described under Related substances (other than the *Z*-isomer).

(1) Dissolve with the aid of ultrasound a quantity of the contents of the capsules containing the equivalent of 100 mg of doxepin in 100 mL of solvent A, filter and dilute 1 volume to 10 volumes with solvent A.

(2) Prepare a solution of *doxepin hydrochloride BPCRS* containing the equivalent of 0.01% w/v doxepin in solvent A.

(3) Dissolve the contents of a vial of *doxepin impurity standard BPCRS* in 25 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuvienthuocngocanh.com/

The chromatographic conditions described under Related substances (other than the Z-isomer) may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity A and impurity C is at least 1.5;

the *resolution* between the peaks due to impurity B and impurity C is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{21}NO$ in the capsules using the declared content of $C_{19}H_{21}NO,HCl$ in *doxepin hydrochloride BPCRS*. Each mg of $C_{19}H_{21}NO,HCl$ is equivalent to 0.884g of $C_{19}H_{21}NO$.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Doxepin Hydrochloride.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of doxepin.

© Crown Copyright 2022

www.webofpharma.com

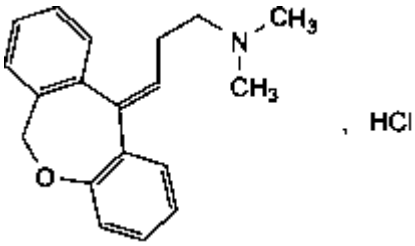
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxepin Hydrochloride

General Notices

(Ph. Eur. monograph 1096)



$C_{19}H_{22}ClNO$ 315.8 *1229-29-4*

Action and use

Monoamine reuptake inhibitor; tricyclic antidepressant.

Preparation

Doxepin Capsules

Ph Eur

DEFINITION

(*E*)-3-(Dibenzo[*b,e*]oxepin-11(6*H*)-ylidene)-*N,N*-dimethylpropan-1-amine hydrochloride.

Content

98.0 per cent to 101.0 per cent of $C_{19}H_{22}ClNO$ (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: C, E.

Second identification: A, B, D, E.

A. Melting point (2.2.14): 185 °C to 191 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in a 1 g/L solution of *hydrochloric acid R* in *methanol R* and dilute to 100.0 mL with the same acid solution. Dilute 5.0 mL to 50.0 mL with a 1 g/L solution of *hydrochloric acid R* in *methanol R*.

Spectral range 230-350 nm.

Absorption maximum At 297 nm.

Specific absorbance at the absorption maximum 128 to 142.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *doxepin hydrochloride CRS*.

D. Dissolve about 5 mg in 2 mL of *sulfuric acid R*. A dark red colour is produced.

E. Solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 1.5 g in *carbon dioxide-free water R* and dilute to 30 mL with the same solvent.

Appearance of solution

Dilute 10 mL of solution S to 25 mL with *water R*. The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity

To 10 mL of solution S add 0.1 mL of *methyl red solution R*. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect them from light.*

Phosphate buffer solution Dissolve 1.42 g of *anhydrous disodium hydrogen phosphate R* in *water R*, adjust to pH 7.7 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture Mix 1 volume of *1 M sodium hydroxide* and 250 volumes of the mobile phase.

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *doxepin for system suitability CRS* (containing impurities A, B and C) in 1.0 mL of mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R1*, phosphate buffer solution, *methanol R1* (20:30:50 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 1.5 times the retention time of doxepin.

Identification of impurities Use the chromatogram supplied with *doxepin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to doxepin (retention time = about 18 min): impurity A = about 0.5; impurity C = about 0.6; impurity B = about 0.7; the peak due to doxepin might show a shoulder caused by the (*Z*)-isomer (impurity D).

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and C, and minimum 1.5 between the peaks due to impurities C and B;

—the chromatogram obtained is similar to the chromatogram supplied with *doxepin for system suitability CRS*.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 1.7;

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

(*Z*)-Isomer

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.12 m, Ø = 4 mm;

— *stationary phase*: spherical *octylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 220 m^2/g and a pore size of 80 nm;

— *temperature*: 50 °C.

Mobile phase Mix 30 volumes of *methanol R* and 70 volumes of a 30 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to the (*E*)-isomer (1^{st} peak) and to the (*Z*)-isomer (2^{nd} peak).

Results:

— calculate the ratio of the area of the peak due to the (*E*)-isomer to the area of the peak due to the (*Z*)-isomer: this ratio is 4.4 to 6.7 (13.0 per cent to 18.5 per cent of the (*Z*)-isomer).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.250 g in a mixture of 5 mL of *anhydrous acetic acid R* and 35 mL of *acetic anhydride R*. Using 0.2 mL of *crystal violet solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from blue to green.

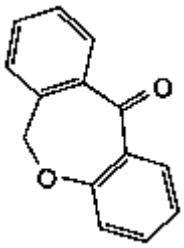
1 mL of *0.1 M perchloric acid* is equivalent to 31.58 mg of $C_{19}H_{22}ClNO$.

STORAGE

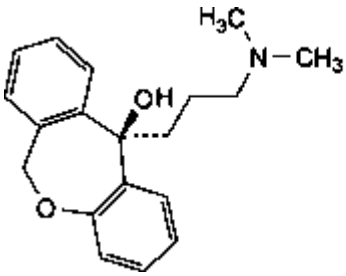
Protected from light.

IMPURITIES

Specified impurities *A, B, C, D.*

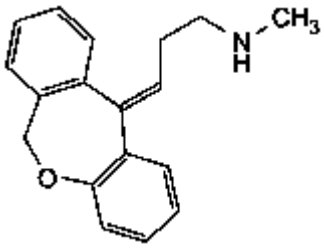


A. dibenzo[*b,e*]oxepin-11(6*H*)-one (doxepinone),



and enantiomer

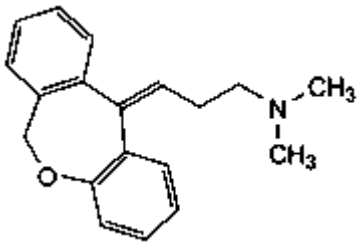
B. (11*RS*)-11-[3-(dimethylamino)propyl]-6,11-dihydrodibenzo[*b,e*]oxepin-11-ol (doxepinol),



C. (*E*)-3-(dibenzo[*b,e*]oxepin-11(6*H*)-ylidene)-*N*-methylpropan-1-amine (desmethyldoxepin),

www.webofpharma.com

https://thuvienthuocngocanh.com/



D. (*Z*)-3-(dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)-*N*,*N*-dimethylpropan-1-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxorubicin for Infusion

General Notices

Doxorubicin for Injection

Action and use

Anthracycline antibacterial; cytotoxic.

DEFINITION

Doxorubicin for Infusion is a sterile material consisting of Doxorubicin Hydrochloride with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of doxorubicin hydrochloride, $C_{27}H_{29}NO_{11}$,HCl

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powder containing 10 mg of Doxorubicin Hydrochloride with 5 mL of 0.01M *hydrochloric acid*, extract 2 mL of the resulting solution with two 5-mL quantities of *ether* and discard the ether layer. Dilute the aqueous solution with *ethanol (96%)* to contain 0.001% w/v of Doxorubicin Hydrochloride. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 550 nm exhibits two maxima, at 234 and 252nm, and two less clearly defined maxima at 288 and 495 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH of a solution containing 0.2% w/v of Doxorubicin Hydrochloride in *Water for Injections*, 4.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. The solutions should be prepared immediately before use.

(1) Dissolve a quantity of the contents of a sealed container to produce a solution containing 0.1% w/v of Doxorubicin Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.002% w/v of each of *doxorubicin hydrochloride BPCRS* and *epirubicin hydrochloride BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3.5 times the retention time of the principal peak.

MOBILE PHASE

50 volumes of *acetonitrile* and 50 volumes of a solution containing 0.288% w/v of *sodium dodecyl sulfate* and 0.225% w/v of *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to doxorubicin and epirubicin is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any other *secondary peak* is not greater than half area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

the sum of the areas of any secondary peaks is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Water

Not more than 4.0% w/w, Appendix IX C. Use 0.1 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing 10 mg of Doxorubicin Hydrochloride per mL (solution A). The endotoxin limit concentration of solution A is 22 IU of endotoxin per mL.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. The solutions should be prepared immediately before use.

(1) Dissolve a quantity of the mixed contents of the 10 containers to produce a solution containing 0.01% w/v of Doxorubicin Hydrochloride.
(2) 0.01% w/v of *doxorubicin hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{29}NO_{11}$,HCl in a container of average content weight using the declared content of $C_{27}H_{29}NO_{11}$,HCl in *doxorubicin hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Doxorubicin Hydrochloride

© Crown Copyright 2022

www.webofpharma.com

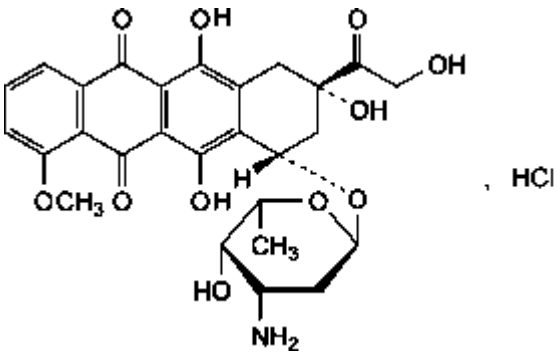
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxorubicin Hydrochloride

General Notices

(Ph. Eur. monograph 0714)



$C_{27}H_{30}ClNO_{11}$ 580.0 *25316-40-9*

Action and use

Anthracycline antibiotic; cytotoxic.

Preparations

Sterile Doxorubicin Concentrate

Doxorubicin for Infusion

Ph Eur

DEFINITION

(8*S*,10*S*)-10-[(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride.

Substance produced by certain strains of *Streptomyces coeruleorubidus* or *Streptomyces peucetius* or obtained by any other means.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

Orange-red, crystalline powder, hygroscopic.

Solubility

Soluble in water, slightly soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *doxorubicin hydrochloride CRS*.

B. Dissolve about 10 mg in 0.5 mL of *nitric acid R*, add 0.5 mL of *water R* and heat over a flame for 2 min. Allow to cool and add 0.5 mL of *silver nitrate solution R1*. A white precipitate is formed.

TESTS

pH (*2.2.3*)

4.0 to 5.5.

Dissolve 50 mg in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 10.0 mg of *doxorubicin hydrochloride CRS* and 10 mg of *epirubicin hydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve 50.0 mg of *doxorubicin hydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm,

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix equal volumes of *acetonitrile R* and a solution containing 2.88 g/L of *sodium laurilsulfate R* and 2.25 g/L of *phosphoric acid R*.

Flow rate 1 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 254 nm.

Injection 5 µL; inject test solution (a) and reference solutions (a) and (b).

Run time 3.5 times the retention time of doxorubicin.

Retention time Doxorubicin = about 8 min.

System suitability Reference solution (a):

— *resolution*: minimum of 2.0 between the peaks due to doxorubicin and to epirubicin.

Limits:

— *any impurity*: not more than the area of the peak due to doxorubicin in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *disregard limit*: 0.1 times the area of the peak due to doxorubicin in the chromatogram obtained with reference solution (b) (0.05 per cent).

Ethanol (*2.4.24, System B*)

Maximum 1.0 per cent.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.100 g.

Bacterial endotoxins (*2.6.14*)

Less than 2.2 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{27}H_{30}ClNO_{11}$.

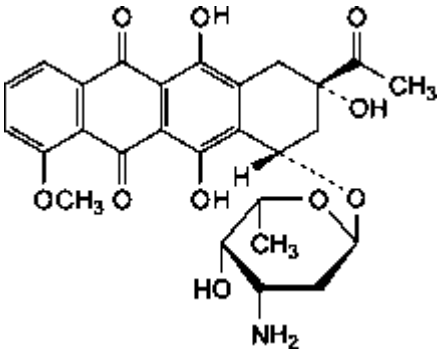
STORAGE

In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

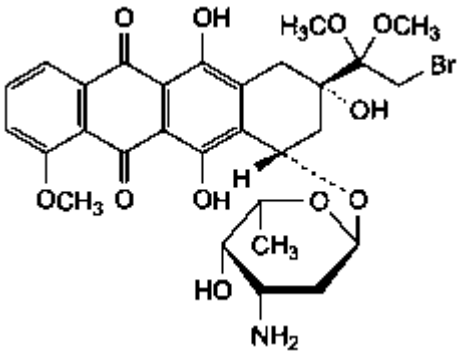
IMPURITIES

www.webofpharma.com

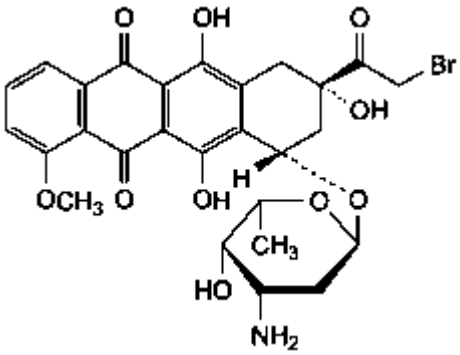
https://thuocngocanh.com/



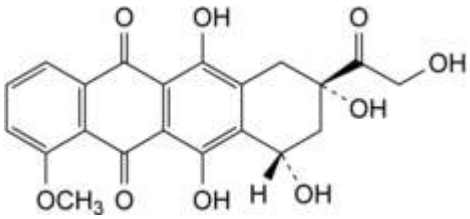
A. (8*S*,10*S*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (daunorubicin),



B. (8*S*,10*S*)-10[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-(2-bromo-1,1-dimethoxyethyl)-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione,



C. (8*S*,10*S*)-10[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-(bromoacetyl)-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione,



D. (8*S*,10*S*)-6,8,10,11-tetrahydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (doxorubicin aglycone, doxorubicinone).

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxycycline Capsules

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Doxycycline Capsules contain Doxycycline Hyclate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of anhydrous doxycycline, $C_{22}H_{24}N_2O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered capsule contents containing the equivalent of 50 mg of anhydrous doxycycline with 100 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.05% w/v of *doxycycline hyclate BPCRS* in *methanol*.

(3) 0.05% w/v each of *doxycycline hyclate BPCRS* and *tetracycline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}. Adjust the pH of a 10% w/v solution of *disodium edetate* to 9.0 with 10M *sodium hydroxide*, spray the plate and allow to dry in a horizontal position for a minimum of 1 hour. Before use, dry the plate in an oven at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and intensity to that in the chromatogram obtained with solution (2).

B. To 0.5 mg of the contents of the capsules add 2 mL of *sulfuric acid*. A yellow colour is produced.

C. The contents of the capsules yield the reactions characteristic *of chlorides*, Appendix VI.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 345 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *doxycycline hyclate BPCRS* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of $C_{22}H_{24}N_2O_8$ in the medium from the absorbances obtained and using the declared content of $C_{22}H_{24}N_2O_8$ in *doxycycline hyclate BPCRS*.

Absorbance

Dissolve the powdered contents of five capsules as completely as possible in sufficient amount of a mixture of 1 volume of 1M *hydrochloric acid* and 99 volumes of *methanol* to produce a solution containing the equivalent of 1.0% w/v of anhydrous doxycycline and filter. The *absorbance* of the filtrate at 490 nm is not more than 0.20, calculated with reference to the dried capsule contents, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.01M *hydrochloric acid*.

Solution A: Suspend 111.6 g of *sodium edetate* in 900 mL of *water*. Adjust to pH 7.0 with *concentrated ammonia* to achieve complete dissolution, then dilute to 1 L with *water*.

(1) Dissolve a quantity of the powdered capsule contents containing the equivalent of 70 mg of anhydrous doxycycline in 80 mL of 0.01M *hydrochloric acid* *and* dilute to 100 mL, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.05% w/v of *doxycycline for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of doxycycline.

MOBILE PHASE

13 volumes of *acetonitrile*, 17 volumes of *water*, 35 volumes of a 6.79% w/v solution of *tetrabutylammonium hydrogen sulfate* previously adjusted to pH 7.0 with *concentrated ammonia* and 35 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions the retention times with reference to doxycycline (retention time about 21 minutes) are impurity C, about 0.4; impurity A, about 0.7, impurity B, about 0.8; and impurity F, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B, C and F using the chromatogram obtained with solution (3) and the chromatogram supplied with *doxycycline for system suitability EPCRS*.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity F is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%);

the areas of any peaks corresponding to impurity B or impurity C are not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the principal peak in the chromatogram obtained with solution (4) (0.2%).

the sum of the areas of any *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Loss on drying

When dried at 105° for 2 hours, the powdered contents of the capsules lose not more than 8.5% of their weight. Use 1 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Weigh and mix the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.01M *hydrochloric acid*.

(1) Dissolve a quantity of the powdered capsule contents containing the equivalent of 0.14 g of anhydrous doxycycline in 200 mL of 0.01M *hydrochloric acid*, filter and dilute 1 volume of the filtrate to 10 volumes.

(2) 0.008% w/v of *doxycycline hyclate BPCRS*.

(3) 0.05% w/v of *doxycycline for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{24}N_2O_8$ in the capsules using the declared content of $C_{22}H_{24}N_2O_8$ in *doxycycline hyclate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous doxycycline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Doxycycline Hyclate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxycycline Dispersible Tablets

General Notices

Dispersible Doxycycline Tablets

Action and use

Tetracycline antibacterial.

DEFINITION

Doxycycline Dispersible Tablets contain Doxycycline Monohydrate in a suitable dispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous doxycycline, $C_{22}H_{24}N_2O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 50 mg of anhydrous doxycycline with 100 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.05% w/v of *doxycycline hyclate BPCRS* in *methanol*.

(3) 0.05% w/v each of *doxycycline hyclate BPCRS* and *tetracycline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}. Adjust the pH of a 10% w/v solution of *disodium edetate* to 9.0 with 10M *sodium hydroxide*, spray the plate and allow to dry in a horizontal position for a minimum of 1 hour. Before use, dry the plate in an oven at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and intensity to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of a solution prepared by dissolving 2 g of *sodium chloride* in 7 mL of *hydrochloric acid* and sufficient *water* to produce 1000 mL, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 276 nm, Appendix II B using the dissolution medium in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *doxycycline hyclate BPCRS* using the dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content anhydrous doxycycline, $C_{22}H_{24}N_2O_8$, in the medium from the absorbances obtained and using the declared content of $C_{22}H_{24}N_2O_8$ in *doxycycline hyclate BPCRS*.

Absorbance

Dissolve a quantity of the powdered tablets as completely as possible in sufficient of a mixture of 1 volume of 1M *hydrochloric acid* and 99 volumes of *methanol* to produce a solution containing the equivalent of 1.0% w/v of anhydrous doxycycline and filter. The *absorbance* of the filtrate at 490 nm is not more than 0.20, calculated with reference to the dried powdered tablets, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D in 0.01M *hydrochloric acid*.

Solution A: Suspend 111.6 g of *sodium edetate* in 900 mL of *water*. Adjust to pH 7.0 with *concentrated ammonia* to achieve complete dissolution, then dilute to 1 L with *water*.

(1) To a quantity of the powdered tablets containing the equivalent of 70 mg of anhydrous doxycycline, add 80 mL of 0.01M *hydrochloric acid*, mix with the aid of ultrasound and dilute to 100 mL. Centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.05% w/v *doxycycline for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

www.webofpharma.com

https://thietbiuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (5µm) (XTerra RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of doxycycline.

MOBILE PHASE

13 volumes of *acetonitrile*, 17 volumes of *water*, 35 volumes of a 6.79 % w/v solution of *tetrabutylammonium hydrogen sulfate* previously adjusted to pH 7.0 with *concentrated ammonia* and 35 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions relative retentions with reference to doxycycline (retention time about 21 minutes) are impurity C, about 0.4; impurity A, about 0.7, impurity B, about 0.8; and impurity F, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B, C and F using the chromatogram obtained with solution (3) and the chromatogram supplied with *doxycycline for system suitability EPCRS*.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity F is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%);

the areas of any peaks corresponding to impurity B or impurity C are not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the principal peak in the chromatogram obtained with solution (4) (0.2%).

the sum of the areas of any *secondary peaks* is not greater than 3 times the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Loss on drying

www.webofpharma.com

https://thuocngocanh.com/

When dried at 60° at a pressure of 2 kPa for 2 hours, the powdered tablets lose not more than 6.0% of their weight. Use 1 g.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.01M *hydrochloric acid*.

(1) To a quantity of the powdered tablets containing the equivalent of 70 mg of anhydrous doxycycline, add 80 mL of 0.01M *hydrochloric acid*, mix with the aid of ultrasound and dilute to 100 mL. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes.

(2) 0.008% w/v of *doxycycline hyclate BPCRS*.

(3) 0.05% w/v *doxycycline for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity A and impurity B is at least 2.0

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{24}N_2O_8$ in the tablets using the declared content of $C_{22}H_{24}N_2O_8$ in *doxycycline hyclate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous doxycycline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Doxycycline Monohydrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

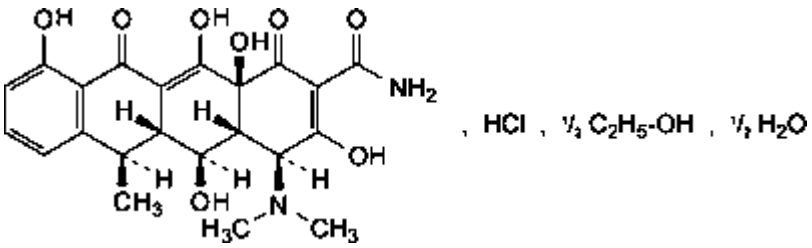
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxycycline Hyclate

General Notices

(Ph. Eur. monograph 0272)



$(C_{22}H_{25}ClN_2O_8),½C_2H_6O,½H_2O$ 512.9 *24390-14-5*

Action and use

Tetracycline antibacterial.

Preparations

Doxycycline Capsules

Doxycycline Tablets

Ph Eur

DEFINITION

(4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride hemiethanol hemihydrate.

Substance obtained from oxytetracycline or metacycline or by any other means.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent of $C_{22}H_{25}ClN_2O_8$ (anhydrous and ethanol-free substance).

CHARACTERS

Appearance

Yellow, hygroscopic, crystalline powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Freely soluble in water and in methanol, sparingly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides and carbonates.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. To about 2 mg add 5 mL of *sulfuric acid R*. A yellow colour develops.

C. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

pH (*2.2.3*)

2.0 to 3.0.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Absorbance (*2.2.25*)

Maximum 0.07 at 490 nm (anhydrous and ethanol-free substance).

Dissolve 0.10 g in a mixture of 1 volume of a 103 g/L solution of *hydrochloric acid R* and 99 volumes of *methanol R* and dilute to 10.0 mL with the same mixture of solvents. Carry out the measurement within 1 h of preparing the solution.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solution A Suspend 111.6 g of *sodium edetate R* in 900 mL of *water for chromatography R*. Adjust to pH 7.0 with *concentrated ammonia R* to achieve complete dissolution, then dilute to 1 L with *water for chromatography R*.

Test solution Dissolve 20.0 mg of the substance to be examined in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution.

Reference solution (a) Dissolve 20.0 mg of *doxycycline hyclate CRS* in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution.

Reference solution (b) Dissolve 5 mg of *doxycycline for system suitability CRS* (containing impurities A, B, C and F) in a 1 g/L solution of *hydrochloric acid R* and dilute to 10 mL with the same solution.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with a 1 g/L solution of *hydrochloric acid R*.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 13 volumes of *acetonitrile R*, 17 volumes of *water for chromatography R*, 35 volumes of a 67.9 g/L solution of *tetrabutylammonium hydrogen sulfate R* previously adjusted to pH 7.0 with *concentrated ammonia R* and 35 volumes of solution A.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of doxycycline.

Identification of impurities Use the chromatogram supplied with *doxycycline for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and F.

Relative retention With reference to doxycycline (retention time = about 21 min): impurity C = about 0.4; impurity A = about 0.7; impurity B = about 0.8; impurity F = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities A and B; minimum 2.0 between the peaks due to impurity B and doxycycline.

Calculation of percentage contents:

— for each impurity, use the concentration of doxycycline hyclate in reference solution (c).

Limits:

— *impurity A*: maximum 2.0 per cent;

— *impurity F*: maximum 1.2 per cent;

— *impurity B*: maximum 0.5 per cent;

— *impurity C*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 3.0 per cent;

— *reporting threshold*: 0.05 per cent.

Ethanol

www.webofpharma.com

https://thuocngocanh.com/

Gas chromatography (2.2.28).

Internal standard solution Dilute 0.50 mL of *propanol R* to 1.0 L with *water R*.

Test solution Dissolve 0.10 g of the substance to be examined in the internal standard solution and dilute to 10.0 mL with the same solution.

Reference solution Dilute 0.5 mL of *anhydrous ethanol R* to 100.0 mL with the internal standard solution. Dilute 1.0 mL of this solution to 10.0 mL with the internal standard solution.

Column:

— *material*: fused silica;

— *size*: *l* = 50 m, Ø = 0.32 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 5 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 37 cm/s.

Split ratio 1:10.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 7	70
	7 - 13	70 → 160
	13 - 15	160
Injection port		200
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to propanol (retention time = about 7 min): ethanol = about 0.6.

Calculate the content of ethanol, taking the density (2.2.5) at 20 °C to be 0.790 g/mL.

Limit:

— *ethanol*: 4.3 per cent to 6.0 per cent.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Water (*2.5.12*)

1.4 per cent to 2.8 per cent, determined on 1.20 g.

Sulfated ash (*2.4.14*)

Maximum 0.4 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 1.14 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{22}H_{25}ClN_2O_8$ taking into account the assigned content of *doxycycline hyclate CRS*.

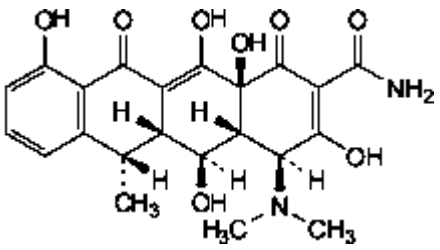
STORAGE

In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Specified impurities *A, B, C, F.*

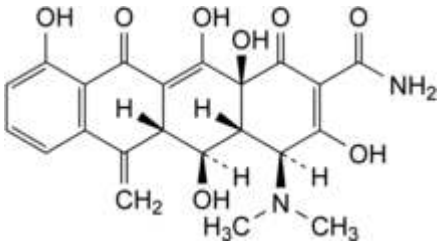
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E.*



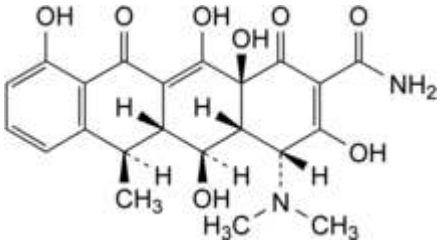
A. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (6-epidoxycycline),

www.webofpharma.com

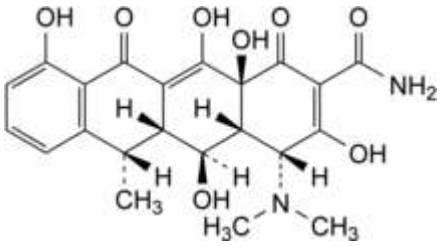
https://thuocngocanh.com/



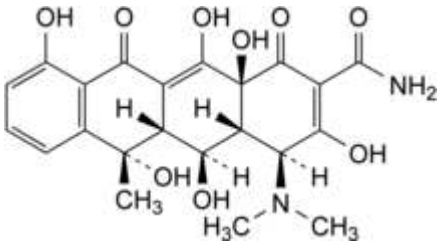
B. (4*S*,4a*R*,5*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (metacycline),



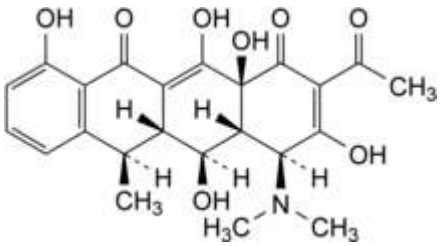
C. (4*R*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epidoxycycline),



D. (4*R*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epi-6-epidoxycycline),



E. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (oxytetracycline),



www.webofpharma.com

https://thuocngocanh.com/

F. (4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-2-acetyl-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione (2-acetyl-2-decarbamoyldoxycycline).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

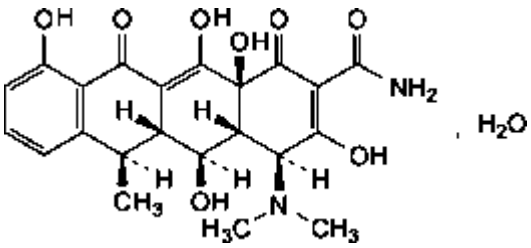
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxycycline Monohydrate

General Notices

(Ph. Eur. monograph 0820)



$C_{22}H_{24}N_2O_8,H_2O$ 462.5 *17086-28-1*

Action and use

Tetracycline antibacterial.

Preparations

Doxycycline Dispersible Tablets

Doxycycline Prolonged-release Capsules

Ph Eur

DEFINITION

(4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide monohydrate.

Substance obtained from oxytetracycline or metacycline or by any other means.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent of $C_{22}H_{24}N_2O_8$ (anhydrous substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

www.webofpharma.com

https://nhathuocngocanh.com/

Solubility

Very slightly soluble in water and in ethanol (96 per cent). It dissolves in dilute solutions of mineral acids and in solutions of alkali hydroxides and carbonates.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. To about 2 mg add 5 mL of *sulfuric acid R*. A yellow colour develops.

C. Water (see Tests).

TESTS

pH (*2.2.3*)

5.0 to 6.5.

Suspend 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Absorbance (*2.2.25*)

Maximum 0.07 at 490 nm (anhydrous substance).

Dissolve 0.10 g in a mixture of 0.5 volumes of *hydrochloric acid R* and 99.5 volumes of *methanol R* and dilute to 10.0 mL with the same mixture of solvents. Carry out the measurement within 1 h of preparing the solution.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solution A Suspend 111.6 g of *sodium edetate R* in 900 mL of *water R*. Adjust to pH 7.0 with *concentrated ammonia R* to achieve complete dissolution, then dilute to 1 L with *water R*.

Test solution Dissolve 20.0 mg of the substance to be examined in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution.

Reference solution (a) Dissolve 20.0 mg of *doxycycline hyclate CRS* in a 1 g/L solution of *hydrochloric acid R* and dilute to 25.0 mL with the same solution.

Reference solution (b) Dissolve 5 mg of *doxycycline for system suitability CRS* (containing impurities A, B, C and F) in a 1 g/L solution of *hydrochloric acid R* and dilute to 10 mL with the same solution.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with a 1 g/L solution of *hydrochloric acid R*.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (5 µm) ;

— *temperature*: 35 °C.

Mobile phase Mix 13 volumes of *acetonitrile R*, 17 volumes of *water R*, 35 volumes of a 67.9 g/L solution of *tetrabutylammonium hydrogen sulfate R* previously adjusted to pH 7.0 with *concentrated ammonia R* and 35 volumes of solution A.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of doxycycline.

Identification of impurities Use the chromatogram supplied with *doxycycline for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and F.

Relative retention With reference to doxycycline (retention time = about 21 min): impurity C = about 0.4; impurity A = about 0.7; impurity B = about 0.8; impurity F = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities A and B; minimum 2.0 between the peaks due to impurity B and doxycycline.

Calculation of percentage contents:

— for each impurity, use the concentration of doxycycline monohydrate in reference solution (c).

Limits:

— *impurity A*: maximum 2.0 per cent;

— *impurity F*: maximum 1.2 per cent;

— *impurity B*: maximum 0.5 per cent;

— *impurity C*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 3.0 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

www.webofpharma.com

https://thuocngocanh.com/

3.6 per cent to 4.6 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.4 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{22}H_{24}N_2O_8$ taking into account the assigned content of *doxycycline hyclate CRS*.

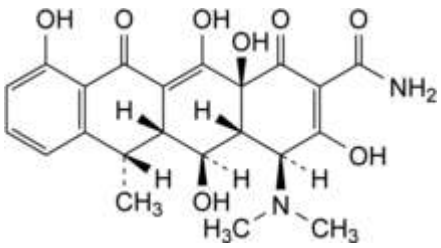
STORAGE

Protected from light.

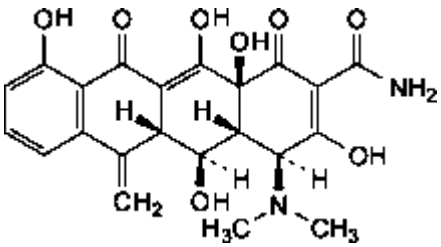
IMPURITIES

Specified impurities *A, B, C, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E.*



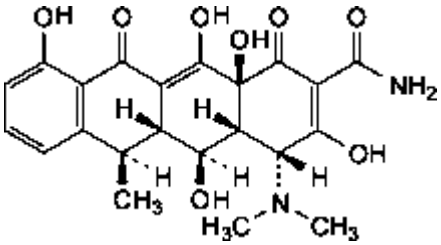
A. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (6-epidoxycycline),



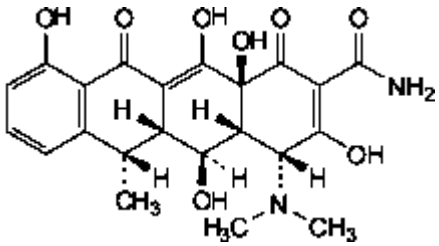
B. (4*S*,4a*R*,5*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (metacycline),

www.webofpharma.com

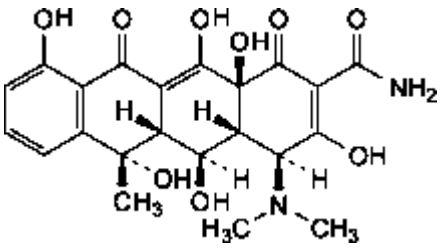
https://thuocngocanh.com/



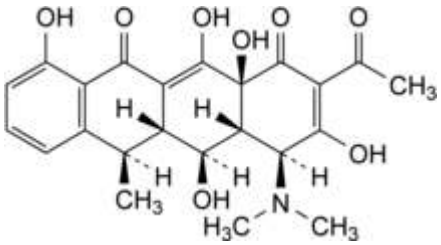
C. (4*R*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epidoxycycline),



D. (4*R*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epi-6-epidoxycycline),



E. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (oxytetracycline),



F. (4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-2-acetyl-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione (2-acetyl-2-decarbamoyldoxycycline).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxycycline Prolonged-Release Capsules

General Notices

Action and use

Tetracycline antibacterial.

Doxycycline Prolonged-Release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

DEFINITION

Doxycycline Prolonged-release Capsules contain Doxycycline Monohydrate and are formulated so as to release the medicament over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Doxycycline Monohydrate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of anhydrous doxycycline, $C_{22}H_{24}N_2O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered capsule contents containing the equivalent of 50 mg of anhydrous doxycycline with 100 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.05% w/v of *doxycycline hyclate BPCRS* in *methanol*.

(3) 0.05% w/v each of *doxycycline hyclate BPCRS* and *tetracycline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*. Adjust the pH of a 10% w/v solution of *disodium edetate* to 9.0 with 10M *sodium hydroxide*, spray the plate and allow to dry in a horizontal position for a minimum of 1 hour. Before use, dry the plate in an oven at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of air and examine under *ultraviolet light (365 nm)*.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and intensity to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Absorbance

Dissolve the contents of five capsules as completely as possible in sufficient of a mixture of 1 volume of 1M *hydrochloric acid* and 99 volumes of *methanol* to produce a solution containing the equivalent of 1.0% w/v of anhydrous doxycycline and filter. The *absorbance* of the filtrate at 490 nm is not more than 0.20, calculated with reference to the dried capsule contents, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D in 0.01M *hydrochloric acid*. Solution A: Suspend 111.6 g of *sodium edetate* in 900 mL of *water*. Adjust to pH 7.0 with *concentrated ammonia* to achieve complete dissolution, then dilute to 1 L with *water*.

(1) Dissolve a quantity of the powdered capsule contents containing the equivalent of 70 mg of anhydrous doxycycline in 80 mL of 0.01M *hydrochloric acid* and dilute to 100 mL, centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.05% w/v *doxycycline for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (5µm) (XTerra RP18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of doxycycline.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

13 volumes of *acetonitrile*, 17 volumes of *water*, 35 volumes of a 6.79 % w/v solution of *tetrabutylammonium hydrogen sulfate* previously adjusted to pH 7.0 with *concentrated ammonia* and 35 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to doxycycline (retention time about 21 minutes) are impurity C, about 0.4; impurity A, about 0.7, impurity B, about 0.8; and impurity F, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B, C and F using the chromatogram obtained with solution (3) and the chromatogram supplied with *doxycycline for system suitability EPCRS*.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity F is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%);

the areas of any peak corresponding to either impurity B or impurity C are not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the principal peak in the chromatogram obtained with solution (4) (0.2%).

the sum of the areas of any *secondary peaks* is not greater than 3 times the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Loss on drying

When dried at 105° for 2 hours, the contents of the capsules lose not more than 5.0% of their weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.01M *hydrochloric acid*.

(1) Dissolve a quantity of the powdered capsule contents containing the equivalent of 70 mg of anhydrous doxycycline in 80 mL of 0.01M *hydrochloric acid* and dilute to 100 mL, filter and dilute 1 volume of the filtrate to 10 volumes.

(2) 0.008% w/v of *doxycycline hyclate BPCRS* in 0.01M *hydrochloric acid*.

(3) 0.05% w/v of *doxycycline for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thietbiuocngocanh.com/

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity A and impurity B is at least 2.0

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{24}N_2O_8$ in the capsules using the declared content of $C_{22}H_{24}N_2O_8$ in *doxycycline hyclate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous doxycycline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Doxycycline Monohydrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxycycline Tablets

General Notices

Action and use

Tetracycline antibacterial.

DEFINITION

Doxycycline Tablets contain Doxycycline Hyclate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of anhydrous doxycycline, $C_{22}H_{24}N_2O_8$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 50 mg of anhydrous doxycycline with 100 mL of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.05% w/v of *doxycycline hyclate BPCRS* in *methanol*.

(3) 0.05% w/v each of *doxycycline hyclate BPCRS* and *tetracycline hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel GF_{254}*. Adjust the pH of a 10% w/v solution of *disodium edetate* to 9.0 with 10M *sodium hydroxide*, spray the plate and allow to dry in a horizontal position for a minimum of 1 hour. Before use, dry the plate in an oven at 110° for 1 hour.

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

6 volumes of *water*, 35 volumes of *methanol* and 59 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and intensity to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.
(b) Use 900 mL of a solution prepared by dissolving 2 g of *sodium chloride* in a solution containing 0.7% v/v of *hydrochloric acid* in *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 276 nm, Appendix II B using the dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *doxycycline hyclate BPCRS* using the dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content anhydrous doxycycline, $C_{22}H_{24}N_2O_8$, in the medium from the absorbances obtained and using the declared content of $C_{22}H_{24}N_2O_8$ in *doxycycline hyclate BPCRS*.

LIMITS

The amount of doxycycline released is not less than 75% (Q) of the stated amount.

Absorbance

Dissolve a quantity of the powdered tablets as completely as possible in sufficient of a mixture of 1 volume of 1M *hydrochloric acid* and 99 volumes of *methanol* to produce a solution containing the equivalent of 1.0% w/v of anhydrous doxycycline and filter. The *absorbance* of the filtrate at 490 nm is not more than 0.20, calculated with reference to the dried powdered tablets, Appendix II B.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D in 0.01M *hydrochloric acid*.

Solution A: Suspend 111.6 g of *sodium edetate* in 900 mL of *water*. Adjust to pH 7.0 with *concentrated ammonia* to achieve complete dissolution, then dilute to 1 L with *water*.

(1) To a quantity of the powdered tablets containing the equivalent of 70 mg of anhydrous doxycycline, add 80 mL of 0.01M *hydrochloric acid*, mix with the aid of ultrasound and dilute to 100 mL, filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes.

www.webofpharma.com

https://thietbiuocngocanh.com/

(3) 0.05% w/v of *doxycycline for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (5µm) (XTerra RP18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35º.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of doxycycline.

MOBILE PHASE

13 volumes of *acetonitrile*, 17 volumes of *water*, 35 volumes of a 6.79 % w/v solution of *tetrabutylammonium hydrogen sulfate* previously adjusted to pH 7.0 with *concentrated ammonia* and 35 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to doxycycline (retention time about 21 minutes) are impurity C, about 0.4; impurity A, about 0.7, impurity B, about 0.8; and impurity F, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 2.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities A, B, C and F using the chromatogram obtained with solution (3) and the chromatogram supplied with *doxycycline for system suitability EPCRS*.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity F is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%);

the areas of any peaks corresponding to impurity B or impurity C are not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the principal peak in the chromatogram obtained with solution (4) (0.2%).

the sum of the areas of any *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying

When dried at 105° for 2 hours, the contents of the tablets lose not more than 8.5% of their weight. Use 1 g.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.01M *hydrochloric acid*.

(1) To a quantity of the powdered tablets containing the equivalent of 70 mg of anhydrous doxycycline, add 80 mL of 0.01M *hydrochloric acid*, mix with the aid of ultrasound and dilute to 100 mL. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes.

(2) 0.008% w/v of *doxycycline hyclate BPCRS*.

(3) 0.05% w/v of *doxycycline for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity A and impurity B is at least 2.0

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{24}N_2O_8$ in the tablets using the declared content of $C_{22}H_{24}N_2O_8$ in *doxycycline hyclate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous doxycycline.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Doxycycline Monohydrate.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

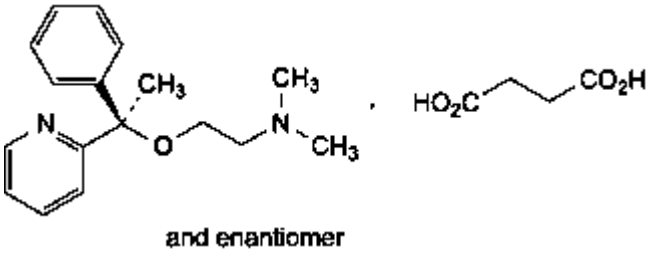
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Doxylamine Succinate

General Notices

(Doxylamine Hydrogen Succinate, Ph. Eur. monograph 1589)



$C_{21}H_{28}N_2O_5$ 388.5 *562-10-7*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

N,N-Dimethyl-2-[(1*RS*)-1-phenyl-1-(pyridin-2-yl)ethoxy]ethanamine hydrogen butanedioate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *doxylamine hydrogen succinate CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.4 g in *water R* and dilute to 20 mL with the same solvent.

Related substances

Gas chromatography (*2.2.28*).

Test solution Dissolve 0.650 g of the substance to be examined in 20 mL of a 10.3 g/L solution of *hydrochloric acid R*. Add 3 mL of a 100 g/L solution of *sodium hydroxide R* and extract with 3 quantities, each of 25 mL, of *methylene chloride R*. Combine the methylene chloride extracts and filter using hydrophobic phase-separation filter paper. Rinse the filter with 10 mL of *methylene chloride R* and combine the rinsings with the methylene chloride extracts. Evaporate the solvent under reduced pressure at a temperature not exceeding 40 °C. Dissolve the residue in 20.0 mL of *anhydrous ethanol R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *anhydrous ethanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *anhydrous ethanol R*.

Reference solution (b) Dissolve 50 mg of *doxylamine for system suitability CRS* (containing impurity C) in 10 mL of a 10.3 g/L solution of *hydrochloric acid R*. Add 1.5 mL of a 100 g/L solution of *sodium hydroxide R* and extract with 3 quantities, each of 25 mL, of *methylene chloride R*. Combine the methylene chloride extracts and filter using hydrophobic phase-separation filter paper. Rinse the filter with 10 mL of *methylene chloride R* and combine the rinsings with the methylene chloride extracts. Evaporate the solvent under reduced pressure at a temperature not exceeding 40 °C. Dissolve the residue in 5.0 mL of *anhydrous ethanol R*.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 1.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 7 mL/min.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Column	0 - 12	160 → 220
	12 - 27	220
Injection port		250
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Identification of impurities Use the chromatogram supplied with *doxylamine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to doxylamine (retention time = about 12 min): impurity C = about 0.96.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity C and doxylamine.

Limits:

— *impurity C*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 2.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 19.43 mg of $C_{21}H_{28}N_2O_5$.

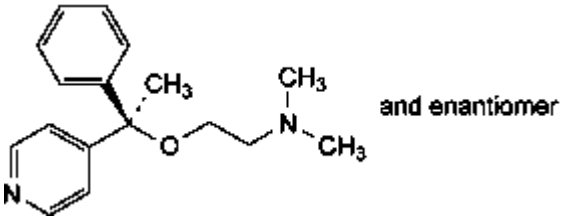
www.webofpharma.com

https://thuocngocanh.com/

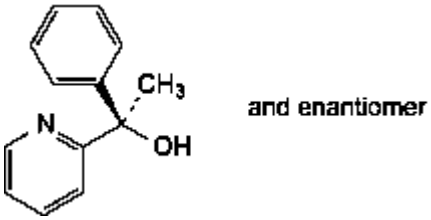
IMPURITIES

Specified impurities C.

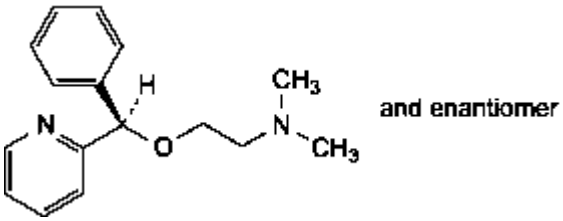
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D.



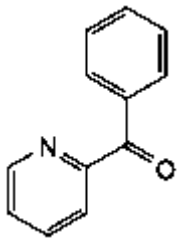
A. *N,N*-dimethyl-2-[(1*RS*)-1-phenyl-1-(pyridin-4-yl)ethoxy]ethanamine,



B. (1*RS*)-1-phenyl-1-(pyridin-2-yl)ethanol,



C. *N,N*-dimethyl-2-[(1*RS*)-1-phenyl-1-(pyridin-2-yl)methoxy]ethanamine,



D. phenyl(pyridin-2-yl)methanone (2-benzoylpyridine).

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dried Aluminium Hydroxide

General Notices

(Hydrated Aluminium Oxide, Ph. Eur. monograph 0311)

Action and use

Antacid.

Preparations

Aluminium Hydroxide Chewable Tablets

Aluminium Hydroxide Oral Suspension

Compound Magnesium Trisilicate Chewable Tablets

Co-magaldrox Oral Suspension

Co-magaldrox Tablets

Ph Eur

DEFINITION

Content

47.0 per cent to 60.0 per cent of Al_2O_3 (M_r 102.0).

CHARACTERS

Appearance

White or almost white, amorphous powder.

Solubility

Practically insoluble in water. It dissolves in dilute mineral acids and in solutions of alkali hydroxides.

IDENTIFICATION

Solution S (see Tests) gives the reaction of aluminium (*2.3.1*).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 2.5 g in 15 mL of *hydrochloric acid R*, heating on a water-bath. Dilute to 100 mL with *distilled water R*.

Appearance of solution

Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution GY_6 (*2.2.2, Method II*).

Alkaline impurities

Shake 1.0 g with 20 mL of *carbon dioxide-free water R* for 1 min and filter. To 10 mL of the filtrate add 0.1 mL of *phenolphthalein solution R*. Any pink colour disappears on the addition of 0.3 mL of *0.1 M hydrochloric acid*.

Neutralising capacity

Carry out the test at 37 °C Disperse 0.5 g in 100 mL of *water R*, heat, add 100.0 mL of *0.1 M hydrochloric acid*, previously heated, and stir continuously; the pH (*2.2.3*) of the solution after 10 min, 15 min and 20 min is not less than 1.8, 2.3 and 3.0 respectively and is at no time greater than 4.5. Add 10.0 mL of *0.5 M hydrochloric acid*, previously heated, stir continuously for 1 h and titrate with *0.1 M sodium hydroxide* to pH 3.5; not more than 35.0 mL of *0.1 M sodium hydroxide* is required.

Chlorides (*2.4.4*)

Maximum 1 per cent.

Dissolve 0.1 g with heating in 10 mL of *dilute nitric acid R* and dilute to 100 mL with *water R*. Dilute 5 mL of the solution to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 1 per cent.

Dilute 4 mL of solution S to 100 mL with *distilled water R*.

Arsenic (*2.4.2, Method A*)

Maximum 4 ppm, determined on 10 mL of solution S.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of bile-tolerant gram-negative bacteria (*2.6.13*).

Absence of *Escherichia coli* (*2.6.13*).

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.800 g in 10 mL of *hydrochloric acid R1*, heating on a water-bath. Cool and dilute to 50.0 mL with *water R*. To 10.0 mL of the solution add *dilute ammonia R1* until a precipitate begins to appear. Add the smallest quantity of *dilute hydrochloric acid R* needed to dissolve the precipitate and dilute to 20 mL with *water R*. Carry out the complexometric titration of aluminium (*2.5.11*).

1 mL of *0.1 M sodium edetate* is equivalent to 5.098 mg of Al_2O_3.

STORAGE

In an airtight container, at a temperature not exceeding 30 °C.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for hydrated aluminium oxide used as adsorbent.

Particle-size distribution (*2.9.31*)

Specific surface area (*2.9.26*)

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dried Aluminium Phosphate

General Notices

(Aluminium Phosphate, Hydrated, Ph. Eur. monograph 1598)

$AlPO_4,xH_2O$ 122.0 (anhydrous substance)

Action and use

Antacid.

Ph Eur

DEFINITION

Content

94.0 per cent to 102.0 per cent of $AlPO_4$ (M_r 122.0) (ignited substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of mineral acids and alkali hydroxides.

IDENTIFICATION

A. Solution S (see Tests) gives reaction (b) of phosphates (*2.3.1*).

B. Solution S gives the reaction of aluminium (*2.3.1*).

TESTS

Solution S

Dissolve 2.00 g in *dilute hydrochloric acid R* and dilute to 100 mL with the same acid.

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

5.5 to 7.2

Shake 4.0 g with *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Chlorides (*2.4.4*)

Maximum 1.3 per cent.

Dissolve 50.0 mg in 10 mL of *dilute nitric acid R* and dilute to 200 mL with *water R*.

Soluble phosphates

Maximum 1.0 per cent, calculated as PO_4^{3-}.

Test solution Stir 5.0 g with 150 mL of *water R* for 2 h. Filter and wash the filter with 50 mL of *water R*. Combine the filtrate and the washings and dilute to 250.0 mL with *water R*. Dilute 10.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (a) Dissolve 28.6 mg of *potassium dihydrogen phosphate R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 5.0 mL with *water R*.

Reference solution (c) Dilute 3.0 mL of reference solution (a) to 5.0 mL with *water R*.

Treat each solution as follows. To 5.0 mL add 4 mL of *dilute sulfuric acid R*, 1 mL of *ammonium molybdate solution R*, 5 mL of *water R* and 2 mL of a solution containing 0.10 g of *4-methylaminophenol sulfate R*, 0.5 g of *anhydrous sodium sulfite R* and 20.0 g of *sodium metabisulfite R* in 100 mL of *water R*. Shake and allow to stand for 15 min. Dilute to 25.0 mL with *water R* and allow to stand for a further 15 min. Measure the absorbance (*2.2.25*) at 730 nm. Calculate the content of soluble phosphates from a calibration curve prepared using reference solutions (a), (b) and (c) after treatment.

Sulfates (*2.4.13*)

Maximum 0.6 per cent.

Dilute 8 mL of solution S to 100 mL with *distilled water R*.

Arsenic (*2.4.2*)

Maximum 1 ppm.

1.0 g complies with limit test A.

Loss on ignition

10.0 per cent to 20.0 per cent, determined on 1.000 g at 800 ± 50 °C.

www.webofpharma.com

https://thuocngocanh.com/

Neutralising capacity

Add 0.50 g to 30 mL of *0.1 M hydrochloric acid* previously heated to 37 °C and maintain at this temperature for 15 min while stirring. The pH (2.2.3) of the mixture after 15 min at 37 °C is 2.0 to 2.5.

ASSAY

Dissolve 0.400 g in 10 mL of *dilute hydrochloric acid R* and dilute to 100.0 mL with *water R*. To 10.0 mL of the solution, add 10.0 mL of *0.1 M sodium edetate* and 30 mL of a mixture of equal volumes of *ammonium acetate solution R* and *dilute acetic acid R*. Boil for 3 min, then cool. Add 25 mL of *ethanol (96 per cent) R* and 1 mL of a freshly prepared 0.25 g/L solution of *dithizone R* in *ethanol (96 per cent) R*. Titrate the excess of sodium edetate with *0.1 M zinc sulfate* until the colour changes to pink.

1 mL of *0.1 M sodium edetate* is equivalent to 12.20 mg of $AlPO_4$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dried Calcium Sulfate

General Notices

Exsiccated Calcium Sulfate; Plaster of Paris; Dried Calcium Sulphate

$CaSO_4,½H_2O$ 145.1 *26499-65-0*

DEFINITION

Dried Calcium Sulfate is prepared by heating powdered gypsum, $CaSO_4,2H_2O$, at about 150° in a controlled manner such that it is substantially converted into the hemihydrate, $CaSO_4,½H_2O$, with minimum production of the anhydrous phases of calcium sulfate. It may contain suitable setting accelerators or decelerators.

CHARACTERISTICS

A white or almost white powder; hygroscopic.

Slightly soluble in *water*; more soluble in dilute mineral acids; practically insoluble in *ethanol (96%)*.

IDENTIFICATION

Yields the reactions characteristic of *calcium salts* and of *sulfates*, Appendix VI.

TESTS

Setting properties

20 g mixed with 10 mL of *water* at 15° to 20° in a cylindrical mould about 2.4 cm in diameter sets in 4 to 11 minutes. The mass thus produced, after standing for 3 hours, possesses sufficient hardness to resist pressure of the fingers at the edges, which retain their sharpness of outline and do not crumble.

Loss on ignition

When ignited to constant weight at red heat, loses 4.5% to 8.0% of its weight. Use 1 g.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dried Ferrous Sulfate

General Notices

Dried Ferrous Sulphate

(Ph. Eur. monograph 2340)

$FeSO_4$ 151.9

Action and use

Treatment of iron-deficiency anaemia.

Preparation

Ferrous Sulfate Prolonged-release Tablets

Ph Eur

DEFINITION

Hydrated ferrous sulfate from which part of the water of hydration has been removed by drying.

Content

86.0 per cent to 90.0 per cent.

CHARACTERS

Appearance

Greyish-white powder.

Solubility

Slowly but freely soluble in water, very soluble in boiling water, practically insoluble in ethanol (96 per cent).

It is oxidised in moist air, becoming brown.

IDENTIFICATION

A. It gives the reactions of sulfates (*2.3.1*).

B. It gives reaction (a) of iron (*2.3.1*).

C. It complies with the limits of the assay.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

pH (2.2.3)

3.0 to 4.0.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Chlorides (2.4.4)

Maximum 300 ppm.

Dissolve 2.5 g in *water R*, add 0.5 mL of *dilute sulfuric acid R* and dilute to 50 mL with *water R*. Dilute 3.3 mL of this solution to 10 mL with *water R* and add 5 mL of *dilute nitric acid R*. Prepare the standard using a mixture of 10 mL of *chloride standard solution (5 ppm Cl) R* and 5 mL of *dilute nitric acid R*. Use 0.15 mL of *silver nitrate solution R2* in this test.

Elemental impurities

Any method that fulfils the requirements of general chapter 2.4.20. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Chromium	100
Cobalt	15
Nickel	70
Vanadium	50
Zinc	50

Ferric ions

Maximum 0.5 per cent.

In a ground-glass-stoppered flask, dissolve 5.00 g in a mixture of 10 mL of *hydrochloric acid R* and 100 mL of *carbon dioxide-free water R*. Add 3 g of *potassium iodide R*, close the flask and allow to stand in the dark for 5 min. Titrate the liberated iodine with *0.1 M sodium thiosulfate*, using 0.5 mL of *starch solution R*, added towards the end of titration, as indicator. Carry out a blank test in the same conditions. Not more than 4.5 mL of *0.1 M sodium thiosulfate* is used.

Manganese

Maximum 0.1 per cent.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Dissolve 1.00 g in a 5 per cent *V/V* solution of *nitric acid R* and dilute to 50.0 mL with the same acid. Dilute 1.0 mL of this solution to 20.0 mL with a 5 per cent *V/V* solution of *nitric acid R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions Prepare the reference solutions using *manganese standard solution (1000 ppm Mn) R*, diluting with a 5 per cent *V/V* solution of *nitric acid R*.

Source Manganese hollow-cathode lamp using a transmission band preferably of 1 nm.

Wavelength 279.5 nm.

Atomisation device Air-acetylene flame.

ASSAY

Dissolve 2.5 g of *sodium hydrogen carbonate R* in a mixture of 150 mL of *water R* and 10 mL of *sulfuric acid R*. When the effervescence ceases, add to the solution 0.140 g of the substance to be examined and dissolve with gentle shaking. Add 0.1 mL of *ferroin R* and titrate with *0.1 M ammonium and cerium nitrate* until the red colour disappears.

1 mL of *0.1 M ammonium and cerium nitrate* is equivalent to 15.19 mg of $FeSO_4$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dried Magnesium Sulfate

General Notices

Dried Epsom Salts; Dried Magnesium Sulphate

Preparation

Magnesium Sulfate Paste

DEFINITION

Dried Magnesium Sulfate contains not less than 62.0% and not more than 70.0% of $MgSO_4$. It may be prepared by drying magnesium sulfate at 100° until it has lost approximately 25% of its weight.

CHARACTERISTICS

A white powder.

Freely soluble in *water*; dissolves more rapidly in hot *water*.

IDENTIFICATION

Yields the reactions characteristic of *magnesium salts* and of *sulfates*, Appendix VI.

TESTS

Acidity or alkalinity

To 10 mL of a 7.5% w/v solution in *carbon dioxide-free water* add 0.05 mL of *phenol red solution*. Not more than 0.2 mL of either *0.01M hydrochloric acid VS* or *0.01M sodium hydroxide VS* is required to change the colour of the solution.

Arsenic

0.33 g dissolved in 25 mL of *water* complies with the *limit test for arsenic*, Appendix VII (3 ppm).

Iron

0.33 g dissolved in 10 mL of *water* complies with the *limit test for iron*, Appendix VII (30 ppm).

Chloride

0.13 g dissolved in 15 mL of *water* complies with the *limit test for chlorides*, Appendix VII (400 ppm).

Insoluble matter

www.webofpharma.com

https://thuocngocanh.com/

7.5 g dissolves in 20 mL of *water*, producing a solution which may be slightly turbid at first but which becomes clear in a few minutes.

ASSAY

Dissolve 0.3 g in 50 mL of *water* and carry out the *complexometric titration of magnesium*, Appendix VIII D. Each mL of *0.1M disodium edetate VS* is equivalent to 12.04 mg of $MgSO_4$.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

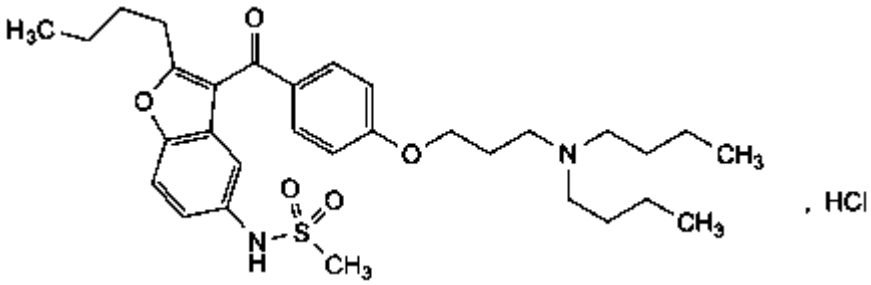
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dronedarone Hydrochloride

General Notices

(Ph. Eur. monograph 3039)



$C_{31}H_{45}ClN_2O_5S$ 593.2 *141625-93-6*

Action and use

Antiarrhythmic.

Preparation

Dronedarone Tablets

Ph Eur

DEFINITION

N-[2-Butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-1-benzofuran-5-yl]methanesulfonamide hydrochloride.

Content

98.0 to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, fine powder.

Solubility

Practically insoluble in water, freely soluble in methanol, soluble in ethanol (96 per cent) and practically insoluble in heptane.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *dronedarone hydrochloride CRS*.

B. Dissolve 32 mg in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (2.3.1); use *methanol R* instead of *water R* to wash the precipitate.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile for chromatography R*, mobile phase A (50:50 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture, using sonication, and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *dronedarone impurity B CRS* in *methanol R* and dilute to 25 mL with the same solvent. Dilute 1 mL of the solution to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *diisopropylcyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: to 2.0 mL of *triethylamine R* add 950 mL of *water for chromatography R*, adjust to pH 4.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	70	30
2 - 17	70 → 60	30 → 40
17 - 27	60	40
27 - 42	60 → 50	40 → 50
42 - 47	50 → 40	50 → 60

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
47 - 60	40	60

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 246 nm.

Injection 25 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to dronedarone (retention time = about 40 min): impurity B = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity B and dronedarone.

Calculation of percentage contents:

— for each impurity, use the concentration of dronedarone hydrochloride in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29).

Solution A To 2.0 mL of *triethylamine R* add 950 mL of *water for chromatography R*, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution Dissolve 50.0 mg of *dronedarone hydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *diisopropylcyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, solution A (50:50 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 288 nm.

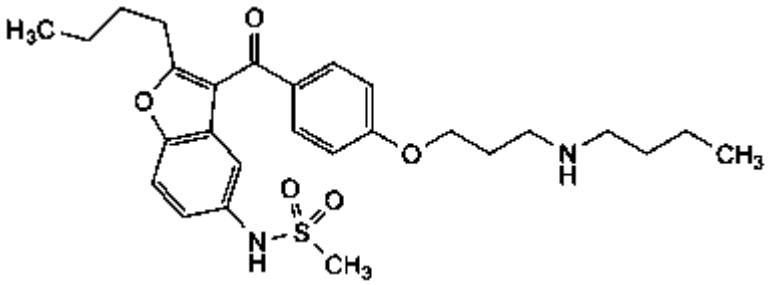
Injection 10 µL.

Run time Twice the retention time of dronedarone (retention time = about 9 min).

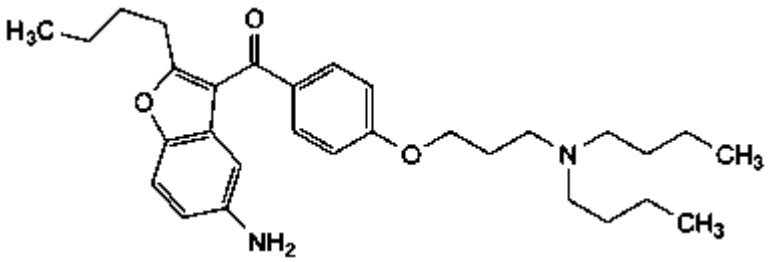
Calculate the percentage content of $C_{31}H_{45}ClN_2O_5S$ taking into account the assigned content of *dronedarone hydrochloride CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



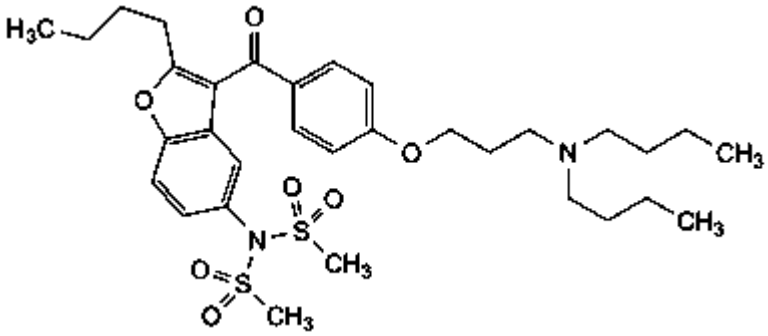
A. *N*-[2-butyl-3-[4-[3-(butylamino)propoxy]benzoyl]-1-benzofuran-5-yl]methanesulfonamide,



B. (5-amino-2-butyl-1-benzofuran-3-yl)[4-[3-(dibutylamino)propoxy]phenyl]methanone,

www.webofpharma.com

https://thuocngocanh.com/



C. *N*-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-1-benzofuran-5-yl]-*N*-(methanesulfonyl)methanesulfonamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dronedarone Tablets

General Notices

(Ph. Eur. monograph 3038)

Action and use

Antiarrhythmic

Ph Eur

DEFINITION

Tablets containing *Dronedarone hydrochloride (3039)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of dronedarone ($C_{31}H_{44}N_2O_5S$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with test solution (b) is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (c).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solution A To 2.0 mL of *triethylamine R* add 950 mL of *water for chromatography R*, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000.0 mL with *water for chromatography R*.

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Crush 20 tablets to obtain a homogeneous powder. Suspend an amount of the powder containing the equivalent of 400 mg of dronedarone in *methanol R* and dilute to 100.0 mL with the same solvent. Sonicate for 5 min and allow to settle for 10 min. Dilute 5.0 mL of the supernatant to 20.0 mL with the mobile phase and filter.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 2 mg of *dronedarone impurity A CRS* and 2 mg of *dronedarone impurity B CRS* in *methanol R* and dilute to 10 mL with the same solvent. Dilute 1 mL of the solution to 20 mL with the mobile phase.

Reference solution (c) Dissolve 53.3 mg of *dronedarone hydrochloride CRS* in *methanol R* and dilute to 25.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *diisopropylcyanosilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile for chromatography R*, solution A (50:50 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 246 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 3.5 times the retention time of dronedarone.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to dronedarone (retention time = about 7.4 min): impurity A = about 0.72; impurity B = about 0.77.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B.

Calculation of percentage contents:

— for each impurity, use the concentration of dronedarone in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.1 per cent.

www.webofpharma.com

https://thuocngocanh.com/

Dissolution[1] (*2.9.3, Apparatus 2*). *Use sinker devices.*

Dissolution medium Dissolve 13.61 g of *potassium dihydrogen phosphate R* in 1000 mL of *water R*. Adjust to pH 4.5 with a 10.3 g/L solution of *hydrochloric acid R* or a 4 g/L solution of *sodium hydroxide R*. Use 1000 mL of the medium.

Rotation speed 75 r/min.

Time 30 min and 90 min.

Analysis Ultraviolet and visible absorption spectrophotometry (*2.2.25*) using a path length of 1 mm.

Test solutions Samples withdrawn from the dissolution vessel and filtered. When a different path length is used, the solutions may be diluted accordingly (e.g. for a path length of 1 cm, 10-fold dilution for 400 mg tablets).

Measure the absorbances of the solutions at the absorption maximum at 288 nm.

Calculate the amount of dissolved dronedarone ($C_{31}H_{44}N_2O_5S$), expressed as a percentage of the content stated on the label, taking the specific absorbance to be 315.

Acceptance criteria:

— *level 1*: 25-50 per cent at 30 min; *Q* = 80 per cent at 90 min;

— *level 2*: the average value of the 12 tablets is within the range 25-50 per cent at 30 min and is not less than 80 per cent at 90 min; none of the units is outside the range 15-60 per cent at 30 min and none of the units is less than 65 per cent of the labelled content at 90 min;

— *level 3*: the average value of the 24 tablets is within the range 25-50 per cent at 30 min and is not less than 80 per cent at 90 min; at 30 min, not more than 2 units are outside the range 15-60 per cent and none is outside the range 5-70 per cent of the labelled content; at 90 min, not more than 2 units are less than 65 per cent of the labelled content and none is less than 55 per cent of the labelled content.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (c).

Detection Spectrophotometer at 288 nm.

Run time Twice the retention time of dronedarone.

System suitability Reference solution (c):

— *symmetry factor*: maximum 2.1;

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

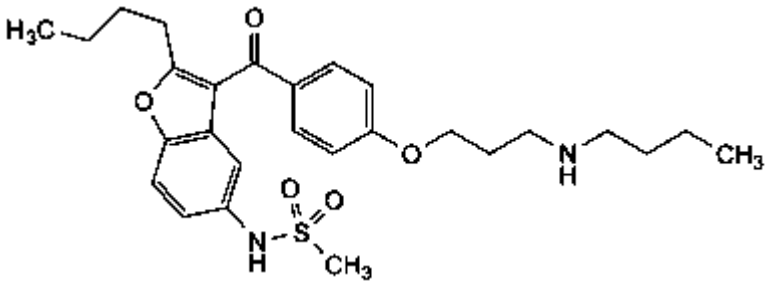
www.webofpharma.com

https://thuocngocanh.com/

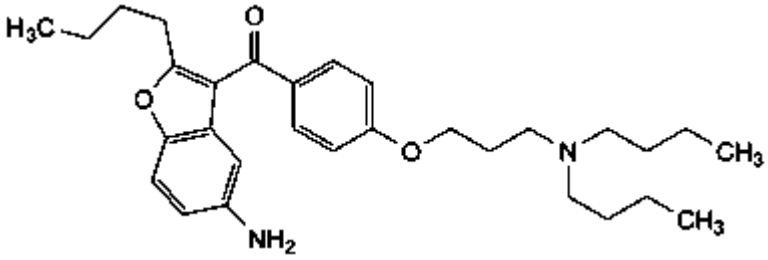
Calculate the percentage content of dronedarone ($C_{31}H_{44}N_2O_5S$) taking into account the assigned content of *dronedarone hydrochloride CRS* and applying a conversion factor of 0.9385.

IMPURITIES

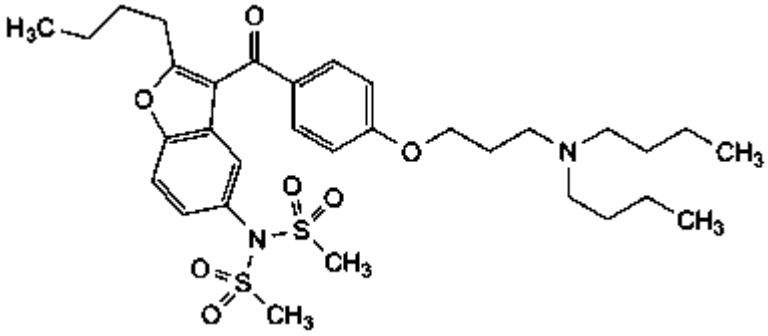
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, B, C.*



A. *N*-[2-butyl-3-[4-[3-(butylamino)propoxy]benzoyl]-1-benzofuran-5-yl]methanesulfonamide,



B. (5-amino-2-butyl-1-benzofuran-3-yl)[4-[3-(dibutylamino)propoxy]phenyl]methanone,



C. *N*-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-1-benzofuran-5-yl]-*N*-(methanesulfonyl)methanesulfonamide.

Ph Eur

1 The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

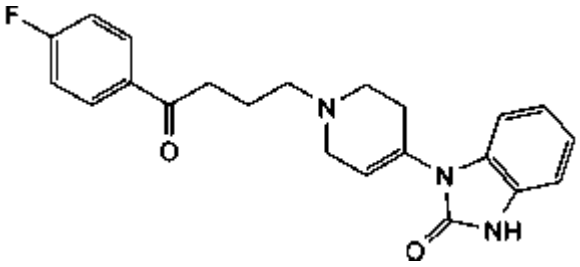
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Droperidol

General Notices

(Ph. Eur. monograph 1010)



$C_{22}H_{22}FN_3O_2$ 379.4 *548-73-2*

Action and use

Dopamine receptor antagonist; $beta_1$-adrenoceptor agonist; alpha-adrenoceptor agonist; neuroleptic.

Preparations

Droperidol Injection

Droperidol Tablets

Ph Eur

DEFINITION

1-[1-[4-(4-Fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in dimethylformamide and in methylene chloride, sparingly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *droperidol CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 30 mg of the substance to be examined in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (a) Dissolve 30 mg of *droperidol CRS* in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (b) Dissolve 30 mg of *droperidol CRS* and 30 mg of *benperidol CRS* in the mobile phase and dilute to 10 mL with the mobile phase.

Plate *TLC silica gel GF_{254} plate R*.

Mobile phase *acetone R*, *methanol R* (10:90 *V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 10 mg in 5 mL of *anhydrous ethanol R*. Add 0.5 mL of *dinitrobenzene solution R* and 0.5 mL of *2 M alcoholic potassium hydroxide R*. A violet colour is produced and becomes brownish-red after 20 min.

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter. To a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate*

www.webofpharma.com

https://thuocngocanh.com/

solution R, add 1.0 mL of the filtrate. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 0.20 g in *methylene chloride R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Test solution Dissolve 0.10 g of the substance to be examined in *dimethylformamide R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 2.5 mg of *droperidol CRS* and 2.5 mg of *benperidol CRS* in *dimethylformamide R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *dimethylformamide R*. Dilute 5.0 mL of this solution to 20.0 mL with *dimethylformamide R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*;

— *mobile phase B*: 10 g/L solution of *tetrabutylammonium hydrogen sulfate R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	0 → 40	100 → 60
15 - 20	40	60
20 - 25	40 → 0	60 → 100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 10 µL.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to droperidol (retention time = about 7 min): impurity A = about 0.2; impurity B = about 0.85; benperidol = about 0.9; impurity C = about 0.95; impurity D = about 1.2; impurity E = about 1.5.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to benperidol and droperidol.

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

— *unspecified impurities*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Using 0.2 mL of *naphtholbenzein solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from orange-yellow to green.

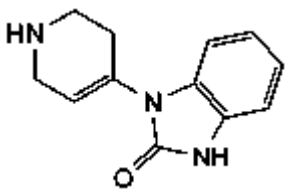
1 mL of *0.1 M perchloric acid* is equivalent to 37.94 mg of $C_{22}H_{22}FN_3O_2$.

STORAGE

Protected from light.

IMPURITIES

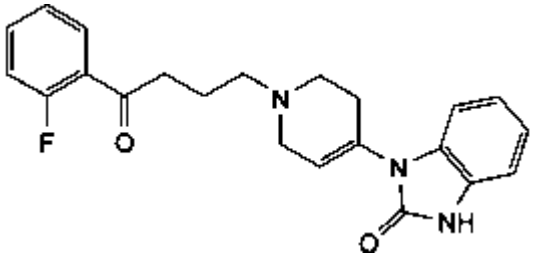
Specified impurities *A, B, C, D, E.*



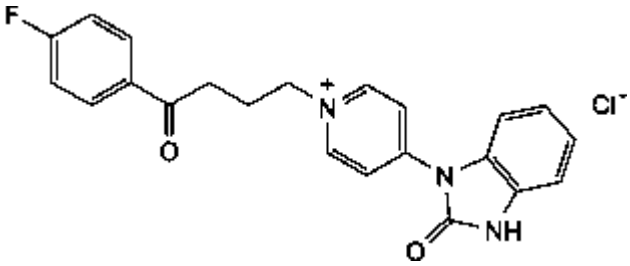
www.webofpharma.com

https://thuocngocanh.com/

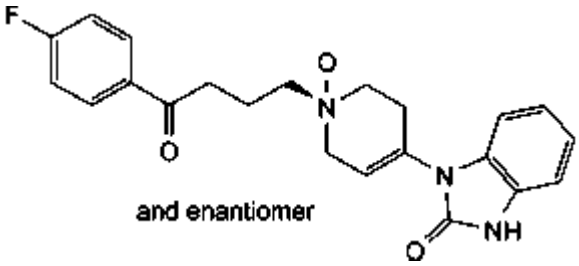
A. 1-(1,2,3,6-tetrahydropyridin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one,



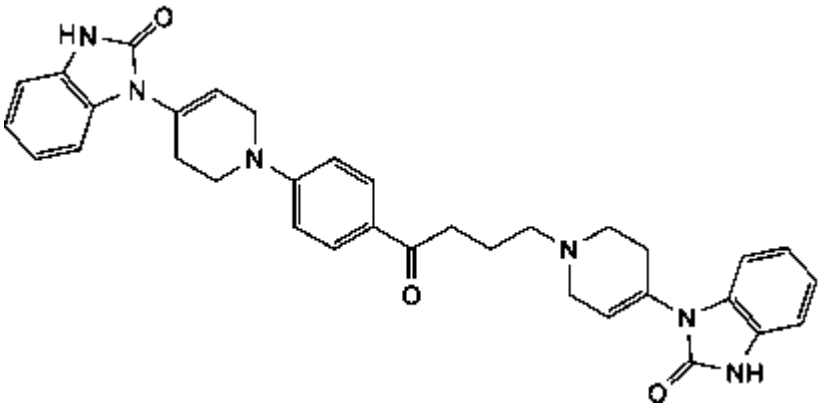
B. 1-[1-[4-(2-fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one,



C. 1-[4-(4-fluorophenyl)-4-oxobutyl]-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)pyridinium chloride,



D. (1*RS*)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1,2,3,6-tetrahydropyridine 1-oxide,



E. 1-[1-[4-[4-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-3,6-dihydropyridin-1(2*H*)-yl]-1-oxobutyl]phenyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Droperidol Injection

General Notices

Action and use

Dopamine receptor antagonist; beta$_1$-adrenoceptor agonist; alpha-adrenoceptor agonist neuroleptic.

DEFINITION

Droperidol Injection is a sterile solution of Droperidol in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of droperidol, $C_{22}H_{22}FN_3O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to droperidol in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 10 volumes of *acetone* and 90 volumes of *methanol* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) shake a volume of the injection containing 10 mg of Droperidol with two successive 10 mL quantities of *dichloromethane* and use the combined extracts. Solution (2) contains 0.05% w/v of *droperidol BPCRS* in *dichloromethane*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.5 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute the injection, if necessary, with a mixture of equal volumes of *dimethylformamide* and a 1% w/v solution of *tetrabutylammonium hydrogen sulfate* to give a solution containing 0.5% w/v of Droperidol. For solution (2) dilute 1 volume of solution (1) to 100 volumes with a mixture of equal volumes of *dimethylformamide* and a 1% w/v solution of *tetrabutylammonium hydrogen sulfate* and dilute 5 volumes of this solution to 20 volumes

www.webofpharma.com

https://thuocngocanh.com/

with the same solvent mixture. Solution (3) contains 0.0025% w/v each of *droperidol BPCRS* and *benperidol EPCRS* in a mixture of equal volumes of *dimethylformamide* and a 1% w/v solution of *tetrabutylammonium hydrogen sulfate*.

The chromatographic procedure may be carried out using (a) a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil C18 BDS 3µ is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute a 1% w/v solution of *tetrabutylammonium hydrogen sulfate* changing by linear gradient to a mixture of 60 volumes of a 1% w/v solution of *tetrabutylammonium hydrogen sulfate* and 40 volumes of *acetonitrile* over 15 minutes, followed by the final mixture for 5 minutes and (c) a detection wavelength of 275 nm. Equilibrate the column with *acetonitrile* for at least 30 minutes before use and then equilibrate at the initial mobile phase composition for at least 30 minutes.

Inject 20 µL of solution (3). When the chromatogram is recorded under the prescribed conditions, the retention times for benperidol and droperidol are about 6.5 minutes and about 7 minutes respectively. The test is not valid unless in the chromatogram obtained with solution (3) the *resolution factor* between the peaks due to droperidol and benperidol is at least 2.0. If necessary, adjust the final concentration of *acetonitrile* in the mobile phase or adjust the time programme for the linear gradient.

When solution (1) is prepared by diluting Droperidol Injection inject 20 µL of a mixture of equal volumes of *dimethylformamide* and a 1% w/v solution of *tetrabutylammonium hydrogen sulfate* as a blank solution. When solution (1) is the undiluted injection, inject 20 µL of *water* as a blank solution. In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%) and the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak obtained with the blank solution and any peak with an area less than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute the injection, if necessary, with *methanol (50%)* to give a solution containing 0.010% w/v of Droperidol. Solution (2) contains 0.010% w/v of *droperidol BPCRS* in *methanol (50%)*. Solution (3) contains 0.0025% w/v of each of *droperidol BPCRS* and *benperidol EPCRS* in *methanol (50%)*.

The chromatographic procedure described under Related substances may be used.

Inject 20 µL of solution (3). When the chromatogram is recorded under the prescribed conditions, the retention times for benperidol and droperidol are about 6.5 minutes and about 7 minutes respectively. The assay is not valid unless in the chromatogram obtained with solution (3) the *resolution factor* between the peaks due to droperidol and benperidol is at least 2.0. If necessary, adjust the final concentration of *acetonitrile* in the mobile phase or adjust the time programme for the linear gradient.

Calculate the content of $C_{22}H_{22}FN_3O_2$ in the injection using the declared content of $C_{22}H_{22}FN_3O_2$ in *droperidol BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Droperidol Tablets

General Notices

Action and use

Dopamine receptor antagonist; beta$_1$-adrenoceptor agonist; alpha-adrenoceptor agonist; neuroleptic.

DEFINITION

Droperidol Tablets contain Droperidol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of droperidol, $C_{22}H_{22}FN_3O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 20 mg of Droperidol with 10 mL of *dichloromethane* for 10 minutes, filter, evaporate the filtrate to dryness and dry the residue for 30 minutes at 90°. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of droperidol (*RS 384*).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to droperidol in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) Withdraw a sample of 10 mL of the medium, filter through a 15-µm membrane filter and immediately measure the *absorbance* of the filtered solution, diluted if necessary with the dissolution medium, at the maximum at 247 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *droperidol BPCRS* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of droperidol, $C_{22}H_{22}FN_3O_2$, in the medium using the declared content of $C_{22}H_{22}FN_3O_2$ in *droperidol BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Droperidol with 20 mL of *dimethylformamide* for 20 minutes, filter and dilute 5 volumes of the filtrate to 10 volumes with a 1% w/v solution of *tetrabutylammonium hydrogen sulfate*.

(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture containing equal volumes of *dimethylformamide* and a 1% w/v solution of *tetrabutylammonium hydrogen sulfate* and further dilute 5 volumes of this solution to 20 volumes with the same solvent mixture.

(3) 0.0025% w/v each of *droperidol BPCRS* and *benperidol EPCRS* in a mixture containing equal volumes of *dimethylformamide* and a 1% w/v solution of *tetrabutylammonium hydrogen sulfate*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil C18 BDS 3µ is suitable).

(b) Use gradient elution and the mobile phases described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 275 nm.

(f) Inject 20 µL of each solution.

(g) Inject 20 µL of a mixture of equal volumes of *dimethylformamide* and a 1% w/v solution of *tetrabutylammonium hydrogen sulfate* as a blank solution.

(h) Equilibrate the column with *acetonitrile* for at least 30 minutes before use and then equilibrate at the initial mobile phase composition for at least 30 minutes.

MOBILE PHASE

Mobile phase A 1% w/v solution of *tetrabutylammonium hydrogen sulfate*.

Mobile phase B 40 volumes of *acetonitrile* and 60 volumes of a 1% w/v solution of *tetrabutylammonium hydrogen sulfate*.

Time (Minutes)	Mobile phase A%	Mobile phase B%	Comment
0-15	100→0	0→100	linear gradient
15-20	0	100	isocratic
20-30	100	0	re-equilibration

SYSTEM SUITABILITY

When the chromatogram is recorded under the prescribed conditions, the retention times for benperidol and droperidol are about 6.5 minutes and about 7 minutes respectively. The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution*

www.webofpharma.com

https://thietbiuocngocanh.com/

between the peaks due to droperidol and benperidol is at least 2.0. If necessary, adjust the final concentration of *acetonitrile* in the mobile phase or adjust the time programme for the linear gradient.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak obtained with the blank solution and any peak with an area less than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Droperidol with 75 mL of *methanol* for 30 minutes, dilute to 100 mL with *methanol*, filter and dilute 10 mL of the resulting solution to 20 mL with *water*.
(2) 0.010% w/v of *droperidol BPCRS* in *methanol (50%)*.
(3) 0.0025% w/v each of *droperidol BPCRS* and *benperidol EPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

Inject solution (3). When the chromatogram is recorded under the prescribed conditions, the retention times for benperidol and droperidol are about 6.5 minutes and about 7 minutes respectively. The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to droperidol and benperidol is at least 2.0. If necessary, adjust the final concentration of *acetonitrile* in the mobile phase or adjust the time programme for the linear gradient.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{22}FN_3O_2$ in the tablets using the declared content of $C_{22}H_{22}FN_3O_2$ in *droperidol BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

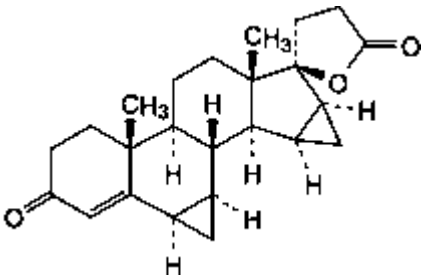
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Drospirenone

General Notices

(Ph. Eur. monograph 2404)



$C_{24}H_{30}O_3$ 366.5 *67392-87-4*

Action and use

Aldosterone receptor antagonist.

Ph Eur

DEFINITION

3-Oxo-6α,7α,15α,16α-tetrahydro-3′*H*,3″*H*-dicyclopropa[6,7:15,16]-17α-pregn-4-en-21,17-carbolactone.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *drospirenone CRS*.

TESTS

Specific optical rotation (2.2.7)

-193 to -187 (dried substance).

Dissolve 0.100 g in *methanol R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the solvent mixture. Use 1.0 mL of this solution to dissolve the contents of a vial of *drospirenone impurity E CRS*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 30.0 mg of *drospirenone CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (d) Dissolve 3 mg of *drospirenone for peak identification CRS* (containing impurity A) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	63	37
2 - 16	63 → 52	37 → 48

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
16 - 23	52	48
23 - 31	52 → 20	48 → 80
31 - 39	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 245 nm.

Injection 10 µL of the test solution and reference solutions (a), (b) and (d).

Identification of impurities Use the chromatogram supplied with *drospirenone for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity E.

Relative retention With reference to drospirenone (retention time = about 22 min): impurity E = about 1.1; impurity A = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to drospirenone and impurity E.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.5;

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

www.webofpharma.com

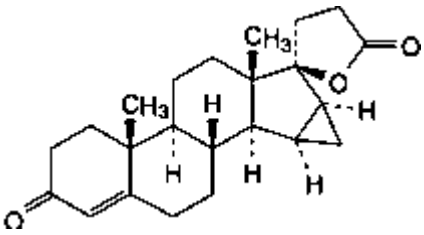
https://thuocngocanh.com/

Calculate the percentage content of $C_{24}H_{30}O_3$ taking into account the assigned content of *drospirenone CRS*.

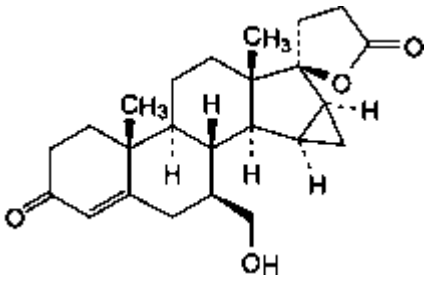
IMPURITIES

Specified impurities A.

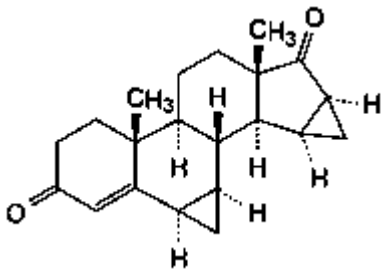
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, F, G, H, I, K.



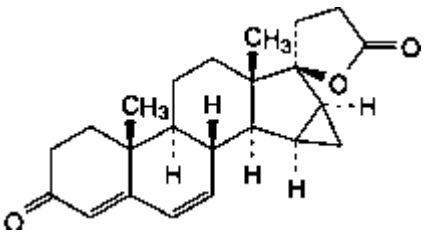
A. 3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (6,7-desmethylenedrospirenone),



B. 7β-(hydroxymethyl)-3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (7β-hydroxymethyl derivative),



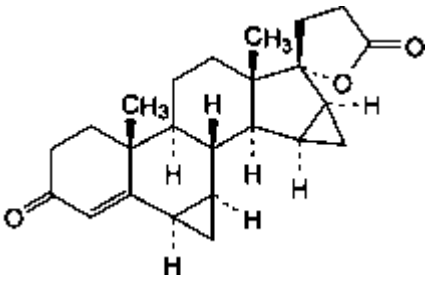
C. 6α,7α,15α,16α-tetrahydro-3′*H*,3″*H* -dicyclopropa[6,7:15,16]androst-4-ene-3,17-dione (17-keto derivative),



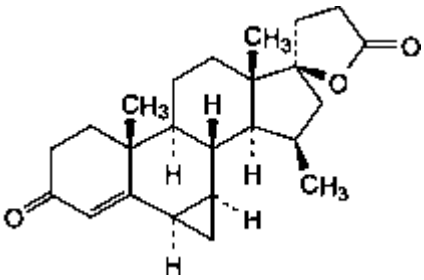
D. 3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregna-4,6-diene-21,17-carbolactone (Δ6-drospirenone),

www.webofpharma.com

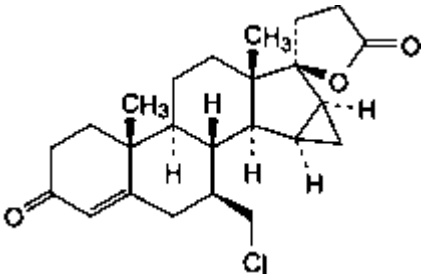
https://thuocngocanh.com/



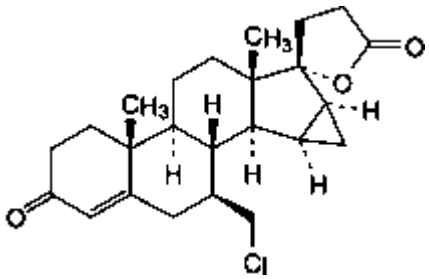
E. 3-oxo-6α,7α,15α,16α-tetrahydro-3′*H*,3″*H* dicyclopropa[6,7:15,16]pregn-4-ene-21,17-carbolactone (17-epidrospirenone),



F. 15β-methyl-3-oxo-6α,7α-dihydro-3′*H*-cyclopropa[6,7]-17α-pregn-4-ene-21,17-carbolactone (3″-16-secodrospirenone),



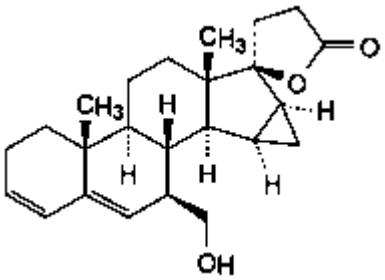
G. 7β-(chloromethyl)-3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregn-4-ene-21,17-carbolactone (3′-chloro-3′,6-secodrospirenone),



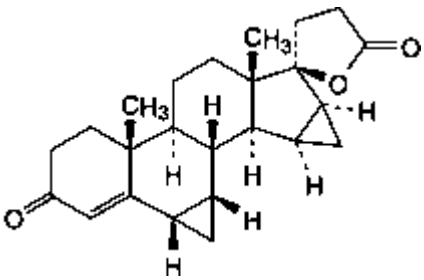
H. 7β-(chloromethyl)-3-oxo-15α,16α-dihydro-3′*H*-cyclopropa[15,16]pregn-4-ene-21,17-carbolactone (3′-chloro-3′,6-seco-17-epidrospirenone),

www.webofpharma.com

https://thuocngocanh.com/



I. 7β-(hydroxymethyl)-15α,16α-dihydro-3′*H*-cyclopropa[15,16]-17α-pregna-3,5-diene-21,17-carbolactone (7β-hydroxymethyldiene derivative),



K. 3-oxo-6β,7β,15α,16α-tetrahydro-3′*H*,3″*H*-dicyclopropa[6,7:15,16]-17α-pregn-4-ene-21,17-carbolactone (6α,7α-drospirenone).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

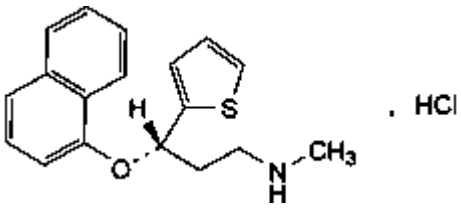
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Duloxetine Hydrochloride

General Notices

(Ph. Eur. monograph 2594)



$C_{18}H_{20}ClNOS$ 333.9 *136434-34-9*

Action and use

Inhibition of 5HT and noradrenaline uptake; antidepressant.

Ph Eur

DEFINITION

(3*S*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine hydrochloride.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, freely soluble in methanol, practically insoluble in hexane.

IDENTIFICATION

Carry out either tests A, B, D or tests B, C, D.

A. Specific optical rotation (2.2.7): + 119 to + 127 (dried substance).

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent. Examine within 30 min of preparing the solution.

www.webofpharma.com

https://thuocngocanh.com/

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *duloxetine hydrochloride CRS*.

C. Enantiomeric purity (see Tests).

D. Dissolve 25 mg in 5 mL of *methanol R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Test solution Dissolve 5.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *duloxetine impurity A CRS* and 5 mg of the substance to be examined in 100 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Add 2.0 mL of *diethylamine R* to 1000 mL of a mixture of 17 volumes of *2-propanol R* and 83 volumes of *hexane R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Relative retention With reference to duloxetine (retention time = about 7 min): impurity A = about 1.3.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to duloxetine and impurity A in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (a).

Limit:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light. Prepare the solutions immediately before use.*

Solvent mixture acetonitrile R, water R (25:75 *V/V*).

Test solution (a) Dissolve 20 mg of the substance to be examined in 200.0 mL of the solvent mixture.

Test solution (b) Dissolve 50.0 mg of the substance to be examined in 100.0 mL of the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 20 mg of duloxetine for system suitability CRS (containing impurity F) in the mobile phase and dilute to 200 mL with the mobile phase. In order to prepare impurities C and D *in situ*, heat the solution at 60 °C for 1 h (solution containing impurities C, D and F).

Reference solution (c) Dissolve 50.0 mg of duloxetine hydrochloride CRS in 100.0 mL of the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical octylsilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 40 °C.

Hexanesulfonate solution Dissolve 10.3 g of sodium hexanesulfonate monohydrate for ion-pair chromatography R in a solution prepared as follows and dilute to 1000.0 mL with the same solution: dissolve 2.9 g (1.7 mL) of phosphoric acid R in 900 mL of water for chromatography R, adjust to pH 2.5 with dilute sodium hydroxide solution R and dilute to 1000 mL with water for chromatography R.

Mobile phase acetonitrile for chromatography R, propanol R, hexanesulfonate solution (13:17:70 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 2.5 times the retention time of duloxetine.

Identification of impurities Use the chromatogram supplied with duloxetine for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C, D and F.

Relative retention With reference to duloxetine (retention time = about 16 min): impurity C = about 0.4; impurity D = about 0.5; impurity F = about 1.1.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities C and D;

— *peak-to-valley ratio*: minimum 4.0, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to duloxetine.

Limits:

— *impurity F*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{18}H_{20}ClNOS$ taking into account the assigned content of *duloxetine hydrochloride CRS*.

STORAGE

Protected from light.

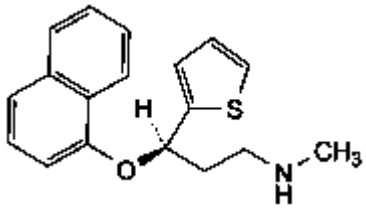
IMPURITIES

Specified impurities *A, F.*

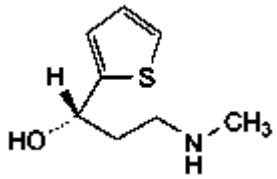
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, G.*

www.webofpharma.com

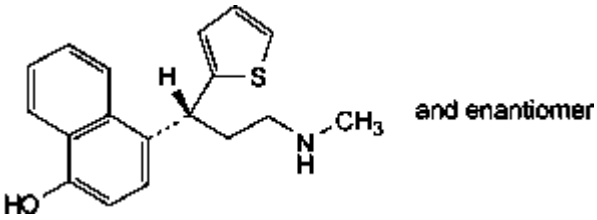
https://thuocngocanh.com/



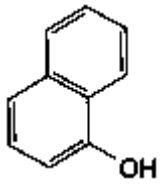
A. (3*R*)-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine,



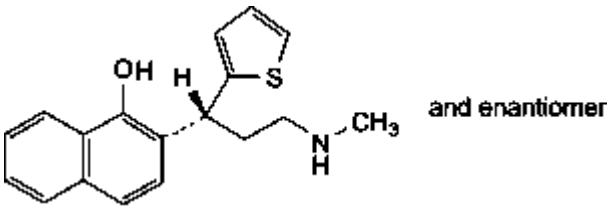
B. (1*S*)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol,



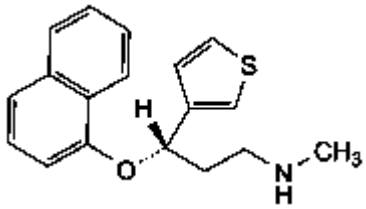
C. 4-[(1*RS*)-3-(methylamino)-1-(thiophen-2-yl)propyl]naphthalen-1-ol,



D. naphthalen-1-ol,



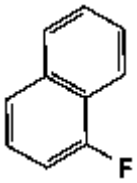
E. 2-[(1*RS*)-3-(methylamino)-1-(thiophen-2-yl)propyl]naphthalen-1-ol,



F. (3*S*)-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-3-yl)propan-1-amine,

www.webofpharma.com

https://thuocngocanh.com/



G. 1-fluoronaphthalene.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

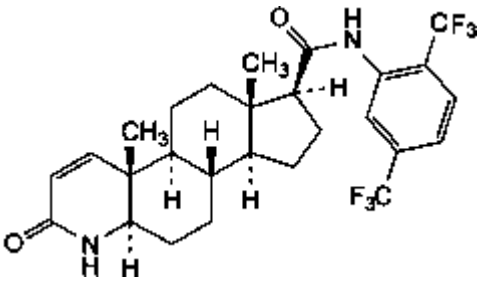
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dutasteride

General Notices

(Ph. Eur. monograph 2641)



$C_{27}H_{30}F_6N_2O_2$ 528.5 *164656-23-9*

Preparation

Dutasteride Capsules

Ph Eur

DEFINITION

N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble or sparingly soluble in anhydrous ethanol.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *dutasteride CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 33.0 to + 39.0 (anhydrous substance).

Dissolve 0.100 g in *anhydrous ethanol R* and dilute to 20.0 mL with the same solvent.

Related substances

A. Liquid chromatography (*2.2.29*).

Solvent mixture *water for chromatography R*, *acetonitrile R1* (40:60 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *dutasteride for system suitability CRS* (containing impurities A, B, C, E, F, G, H and I) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of *dutasteride CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase Mix 0.25 volumes of *trifluoroacetic acid R*, 480 volumes of *water for chromatography R* and 520 volumes of *acetonitrile R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time 1.6 times the retention time of dutasteride.

Identification of impurities Use the chromatogram supplied with *dutasteride for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, E, F and G.

Relative retention With reference to dutasteride (retention time = about 36 min): impurity A = about 0.10; impurity B = about 0.11; impurity C = about 0.4; impurity E = about 0.9; impurity F = about 1.1; impurity G = about 1.2.

www.webofpharma.com

https://thuocngocanh.com/

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity E and dutasteride and minimum 1.5 between the peaks due to impurities A and B in the chromatogram obtained with reference solution (b);

— *signal-to-noise ratio*: minimum 30 for the peak due to dutasteride in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.7; impurity F = 3.0;

— for each impurity, use the concentration of dutasteride in reference solution (a).

Limits:

— *impurity F*: maximum 0.4 per cent;

— *impurities E, G*: for each impurity, maximum 0.3 per cent;

— *impurities A, C*: for each impurity, maximum 0.2 per cent;

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent.

B. Liquid chromatography (2.2.29) as described in test A for related substances with the following modifications.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *acetonitrile R1* (20:80 *V/V*).

Injection 10 µL of the test solution and reference solutions (a) and (b).

Run time 5 times the retention time of dutasteride.

Identification of impurities Use the chromatogram supplied with *dutasteride for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities H and I.

Relative retention With reference to dutasteride (retention time = about 4 min): impurity H = about 3.4; impurity I = about 3.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities H and I.

www.webofpharma.com

https://thuocngocanh.com/

Calculation of percentage contents:

— for each impurity, use the concentration of dutasteride in reference solution (a).

Limits:

— *impurity I*: maximum 0.5 per cent;

— *impurity H*: maximum 0.3 per cent;

— *unspecified impurities eluting after dutasteride*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent.

Limit:

— *total for tests A and B*: maximum 1.5 per cent.

Water (2.5.32)

Maximum 0.2 per cent, determined on 0.100 g using the evaporation technique at 180 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in test A for related substances with the following modification.

Injection 10 µL of the test solution and reference solution (c).

Calculate the percentage content of $C_{27}H_{30}F_6N_2O_2$ taking into account the assigned content of *dutasteride CRS*.

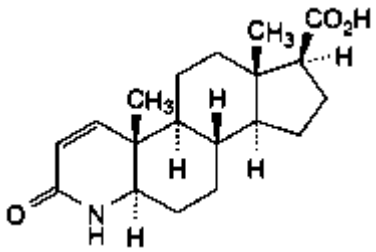
IMPURITIES

Specified impurities *A, B, C, E, F, G, H, I*.

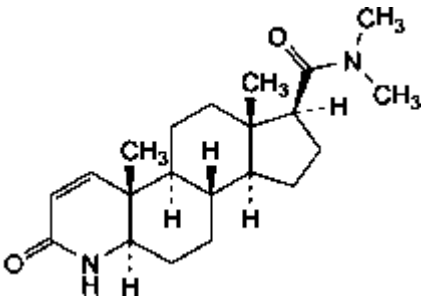
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D*.

www.webofpharma.com

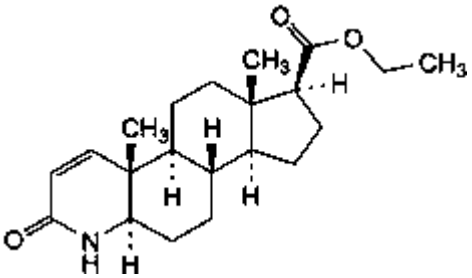
https://thuocngocanh.com/



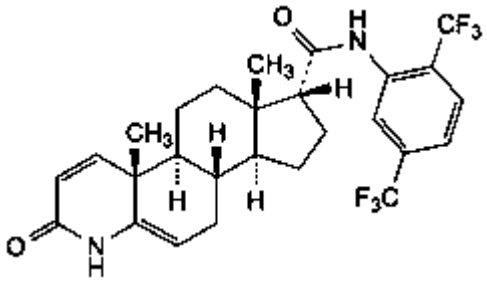
A. 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylic acid,



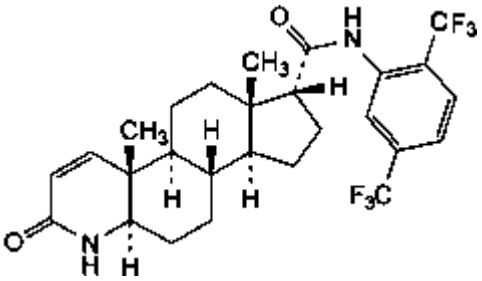
B. *N*,*N*-dimethyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide,



C. ethyl 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylate,



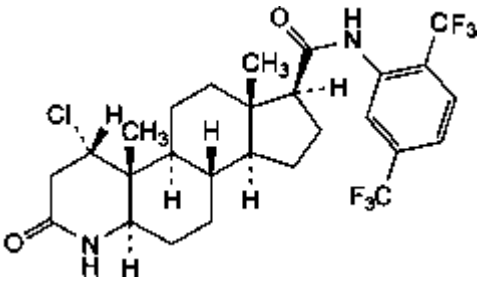
D. *N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5-diene-17α-carboxamide,



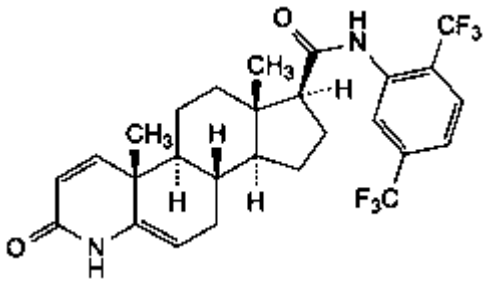
E. *N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androst-1-ene-17α-carboxamide,

www.webofpharma.com

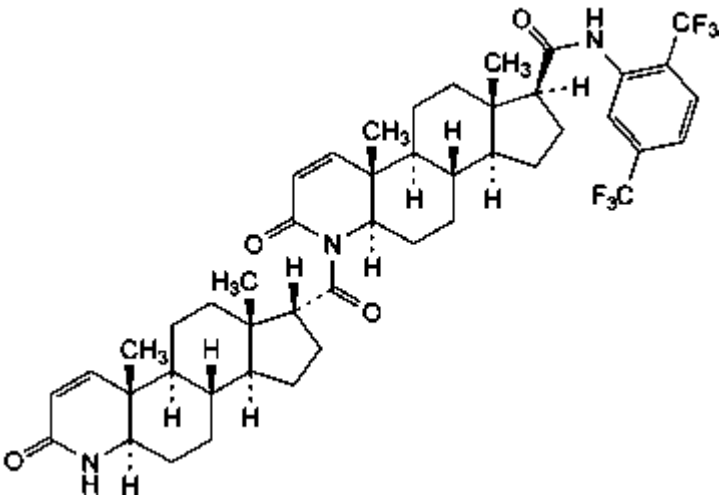
https://thuocngocanh.com/



F. *N*-[2,5-bis(trifluoromethyl)phenyl]-1α-chloro-3-oxo-4-aza-5α-androstane-17β-carboxamide,



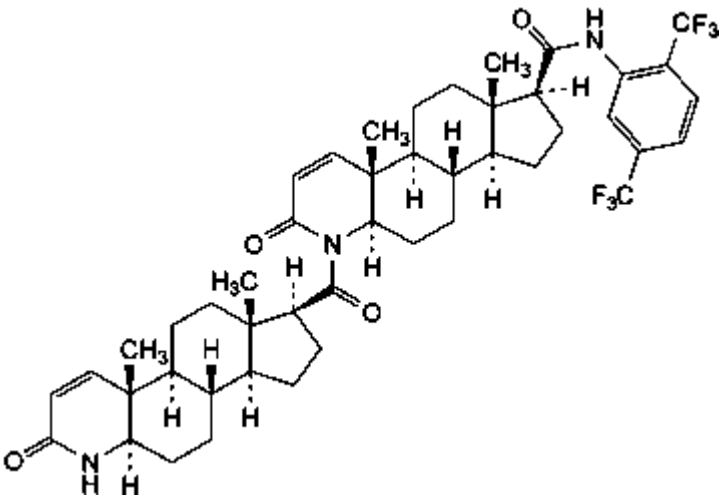
G. *N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5-diene-17β-carboxamide,



H. *N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-[3-oxo-4-aza-5α-androst-1-ene-17α-carbonyl]-4-aza-5α-androst-1-ene-17β-carboxamide (dutasteride dimer 1),

www.webofpharma.com

https://thuocngocanh.com/



I. *N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-[3-oxo-4-aza-5α-androst-1-ene-17β-carbonyl]-4-aza-5α-androst-1-ene-17β-carboxamide (dutasteride dimer 2).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dutasteride Capsules

General Notices

Action and use

5-Alpha reductase inhibitor; treatment of benign prostatic hyperplasia.

DEFINITION

Dutasteride Capsules contain Dutasteride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of dutasteride, $C_{27}H_{30}F_6N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the test for Related substances, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (5).

B. In the test for Dissolution, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use a medium of 450 mL of 0.1M *hydrochloric acid* containing 0.16% w/v *pepsin* for the first 25 minutes, followed by addition of 450 mL of 0.1M *hydrochloric acid* with 4% w/v *sodium dodecyl sulfate* for the remainder of the dissolution test.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 40 volumes of *water* and 60 volumes of *acetonitrile*

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute the filtrate, if necessary, with a 2% w/v solution of *sodium dodecyl sulfate* in 0.1M *hydrochloric acid* to produce a solution expected to contain 0.00005% w/v of Dutasteride.

(2) 0.00005% w/v of *dutasteride EPCRS* in a 2% w/v solution of *sodium dodecyl sulfate* in 0.1M *hydrochloric acid*.

www.webofpharma.com

https://thuocngocanh.com/

(3) To 1 volumes of a 0.01% w/v solution of *dutasteride EPCRS* in solution A, add 1 volumes of a 0.07% w/v solution of *butylated hydroxytoluene* in *methanol* and dilute to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.0 mm) packed with *phenylsilyl silica gel for chromatography* (3.5 µm) (Zorbax SB-Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 50 µL of each solution.

45 volumes of *water* and 55 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dutasteride and butylated hydroxytoluene is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of dutasteride, $C_{27}H_{30}F_6N_2O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{27}H_{30}F_6N_2O_2$ in *dutasteride EPCRS*.

LIMITS

The amount of $C_{27}H_{30}F_6N_2O_2$ released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the capsule contents in the mobile phase to produce a solution containing 0.001% w/v of Dutasteride.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.002% w/v of *dutasteride for system suitability EPCRS*.

(4) Dilute 1 volumes of solution (2) to 10 volumes with the mobile phase.

(5) 0.001% w/v solution of *dutasteride EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5µm) (Zorbax SB-CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for twice the retention time of dutasteride.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

10 volumes of *propan-2-ol* and 90 volumes of *hexane*.

When the chromatograms are recorded under the prescribed conditions, the retention relative to dutasteride (retention time, about 26 min) of impurity E is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dutasteride and impurity E is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Carry out the method for *liquid chromatography*, Appendix III D, using solution A described under Dissolution.

(1) Transfer 1 capsule to a 50 mL volumetric flask, add 10 mL of solution A and cut the capsule, taking care to rinse the cutting tool with solution A. Add sufficient solution A to produce a solution containing 0.001% w/v of Dutasteride, allow to stand at room temperature for 30 minutes, shake with the aid of ultrasound for 15 minutes and filter.
(2) 0.001% w/v of *dutasteride EPCRS* in solution A.
(3) To 1 volumes of a 0.01% w/v solution of *dutasteride EPCRS* in solution A, add 1 volumes of a 0.07% w/v solution of *butylated hydroxytoluene* in *methanol* and dilute to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to dutasteride and butylated hydroxytoluene is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of $C_{27}H_{30}F_6N_2O_2$, in each capsule from the chromatograms obtained and using the declared content of $C_{27}H_{30}F_6N_2O_2$ in *dutasteride EPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

www.webofpharma.com

https://thietbiuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include Impurities A, B, C and E listed under *Dutasteride*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

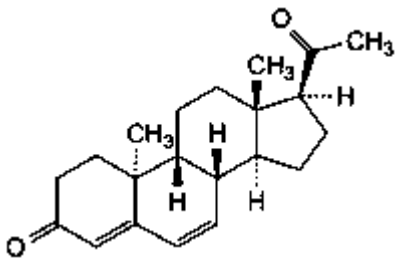
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dydrogesterone

General Notices

(Ph. Eur. monograph 2357)



$C_{21}H_{28}O_2$ 312.5 *152-62-5*

Action and use

Progestogen.

Preparation

Dydrogesterone Tablets

Ph Eur

DEFINITION

9β,10α-Pregna-4,6-diene-3,20-dione.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison dydrogesterone CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of dydrogesterone for impurity A identification CRS in 1 mL of test solution (a).

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 10 mg of the substance to be examined in 30 mL of ethanol (96 per cent) R. Add 1 mL of an 8.4 g/L solution of sodium hydroxide R and heat at 85 °C for 10 min. Cool to room temperature, add 1 mL of a 20.6 g/L solution of hydrochloric acid R, add 20 mL of acetonitrile R and 2 mg of dydrogesterone impurity B CRS, dilute to 100 mL with water R and mix. This solution contains dydrogesterone and impurities B and C.

Reference solution (d) Dissolve 20.0 mg of dydrogesterone CRS in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3 µm);

— *temperature*: 40 °C.

Mobile phase acetonitrile R, ethanol (96 per cent) R, water for chromatography R (21:25:54 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm and, for impurity A, at 385 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Run time Twice the retention time of dydrogesterone.

Identification of impurities Use the chromatogram supplied with dydrogesterone for impurity A identification CRS and the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B and C.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to dydrogesterone (retention time = about 13 min): impurity A = about 0.9; impurity B = about 1.1; impurity C = about 1.2.

System suitability:

— *resolution at 280 nm*: minimum 4.5 between the peaks due to dydrogesterone and impurity B and minimum 1.5 between the peaks due to impurity B and impurity C in the chromatogram obtained with reference solution (c);

— *peak-to-valley ratio at 385 nm*: minimum 2.0, where H_p = height above the baseline of the peak due to dydrogesterone and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 1.9;

— for each impurity, use the concentration of dydrogesterone in reference solution (b) and the area of the principal peak recorded at 280 nm.

Limits:

— *impurity C*: maximum 0.3 per cent;

— *impurity A at 385 nm*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 280 nm.

Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{21}H_{28}O_2$ taking into account the assigned content of *dydrogesterone CRS*.

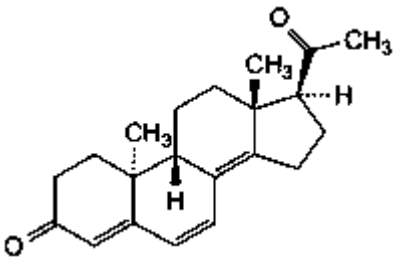
www.webofpharma.com

https://thuathuocngocanh.com/

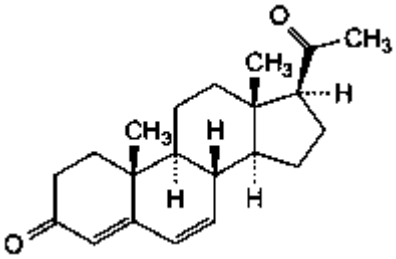
IMPURITIES

Specified impurities *A, C.*

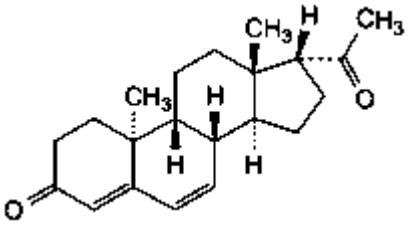
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B.*



A. 9β,10α-pregna-4,6,8(14)-triene-3,20-dione,



B. pregna-4,6-diene-3,20-dione,



C. 9β,10α,17α-pregna-4,6-diene-3,20-dione.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Dydrogesterone Tablets

General Notices

Action and use

Progestogen.

DEFINITION

Dydrogesterone Tablets contain Dydrogesterone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of dydrogesterone, $C_{21}H_{28}O_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 60 mg of Dydrogesterone with 20 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of dydrogesterone *(RS 118)*.

TESTS

Related substances

Carry out the method for *gas chromatography*, Appendix III B.

(1) Extract a quantity of the powdered tablets containing 20 mg of Dydrogesterone with 50 mL of a 0.020% w/v solution of *1,2,3,4-tetraphenylcyclopenta-1,3-diene* (internal standard) in *chloroform* and filter.
(2) Extract a quantity of the powdered tablets containing 20 mg of Dydrogesterone with 20 mL of *chloroform*, filter, evaporate to dryness using a rotary evaporator and dissolve the residue in 1 mL of *chloroform*.
(3) Extract a quantity of the powdered tablets containing 20 mg of Dydrogesterone with 20 mL of a 0.020% w/v solution of *1,2,3,4-tetraphenylcyclopenta-1,3-diene* (internal standard) in *chloroform*, filter, evaporate to dryness using a rotary evaporator and dissolve the residue in 1 mL of *chloroform*.
(4) Dilute 1 volume of solution (1) to 10 volumes with a 0.020% w/v solution of *1,2,3,4-tetraphenylcyclopenta-1,3-diene* (internal standard) in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a glass column (1.5 m × 2.5 mm) packed with *acid-washed, silanised diatomaceous support* (100 to 120 mesh) coated with 3% w/w of *cyanopropyl methyl silicone fluid* (SP-2300 is suitable).

(b) Use *helium* as the carrier gas at 1.5 mL per minute.

(c) Use isothermal conditions maintained at 240°.

(d) Use an inlet temperature of 240°.

(e) Use a flame ionisation detector at a temperature of 240°.

(f) Inject 1 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (1), the *resolution* between the peaks due to dydrogesterone and 1,2,3,4-tetraphenylcyclopenta-1,3-diene is at least 1.5.

LIMITS

In the chromatogram obtained with solution (3), the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than the ratio of the area of the peak due to dydrogesterone to the area of the peak due to the internal standard in the chromatogram obtained with solution (1) (2%).

Disregard any *secondary peak* with an area less than the area of the peak due to dydrogesterone in the chromatogram obtained with solution (4) (0.2%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 10 mg of Dydrogesterone for 15 minutes with 70 mL of *methanol*, dilute to 200 mL with *methanol* and filter. Dilute 5 mL of the filtrate to 100 mL with *methanol* and measure the *absorbance* of the resulting solution at the maximum at 286 nm, Appendix II B. Calculate the content of $C_{21}H_{28}O_2$ taking 845 as the value of *A* (1%, 1 cm) at the maximum at 286 nm.

STORAGE

Dydrogesterone Tablets should be protected from light.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

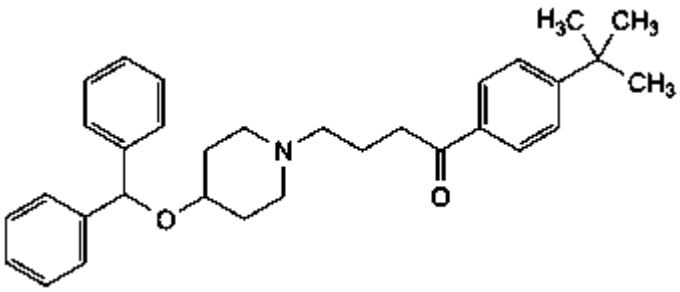
https://thuathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ebastine

General Notices

(Ph. Eur. monograph 2015)



$C_{32}H_{39}NO_2$ 469.7 *90729-43-4*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

1-(4-*tert*-Butylphenyl)-4-[4-(diphenylmethoxy)piperidin-1-yl]butan-1-one.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in methylene chloride, sparingly soluble in methanol.

mp

About 86 °C.

IDENTIFICATION

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison ebastine CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solution A Dilute 12 mL of phosphoric acid R and 12 mL of diethylamine R in 800 mL of water for chromatography R, adjust to pH 6.0 with diethylamine R and dilute to 1000 mL with water for chromatography R.

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of bis(diphenylmethyl) ether R (impurity H) in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 0.5 mL of the solution to 5.0 mL with the test solution. Dilute 3.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase Solution A, methanol R2, acetonitrile R1 (20:38:42 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 15 °C.

Injection 10 µL.

Run time 1.5 times the retention time of ebastine.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity H.

Relative retention With reference to ebastine (retention time = about 27 min): impurity H = about 0.9.

System suitability Reference solution (a):

— resolution: minimum 2 between the peaks due to impurity H and ebastine.

Calculation of percentage contents:

www.webofpharma.com

https://thuocngocanh.com/

— for each impurity, use the concentration of ebastine in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Sulfates (*2.4.13*)

Maximum 100 ppm.

Suspend 2.5 g in 25 mL of *dilute nitric acid R*. Boil under a reflux condenser for 10 min. Cool and filter.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 46.97 mg of $C_{32}H_{39}NO_2$.

STORAGE

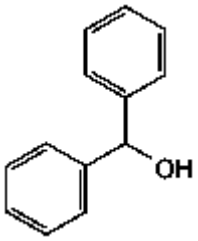
Protected from light.

IMPURITIES

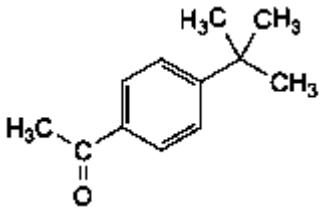
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G, H.

www.webofpharma.com

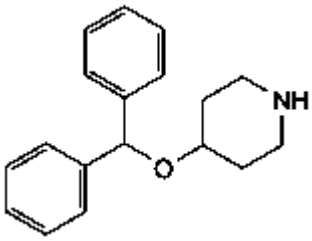
https://thuocngocanh.com/



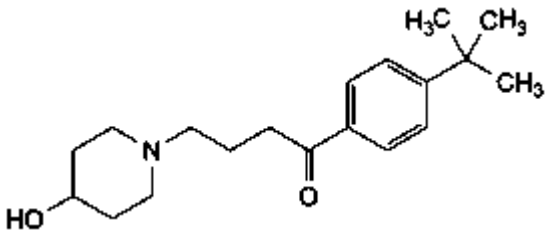
A. diphenylmethanol (benzhydrol),



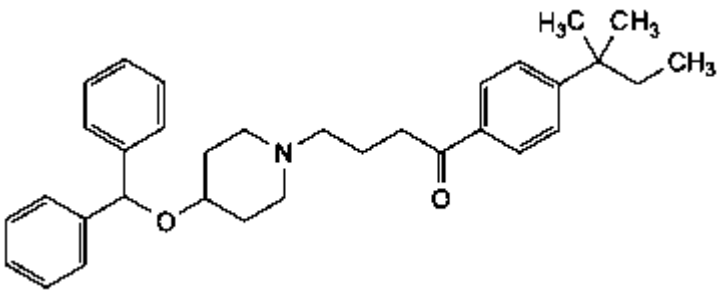
B. 1-(4-*tert*-butylphenyl)ethan-1-one,



C. 4-(diphenylmethoxy)piperidine,



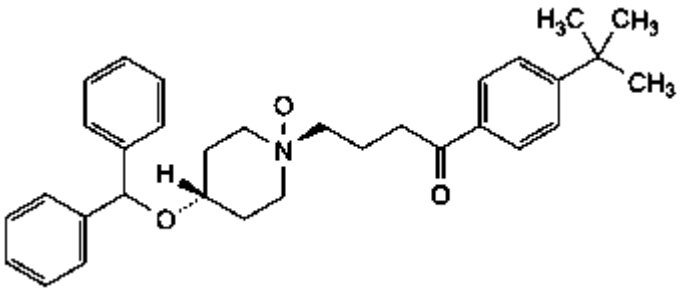
D. 1-(4-*tert*-butylphenyl)-4-(4-hydroxypiperidin-1-yl)butan-1-one,



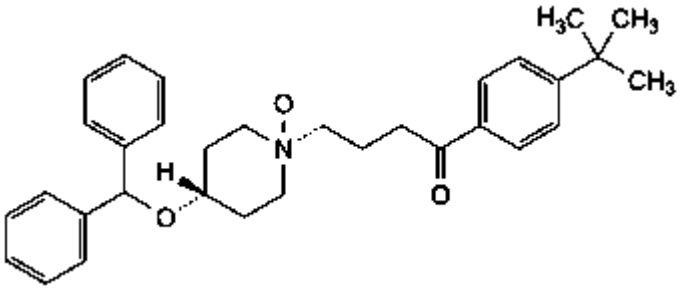
E. 4-[4-(diphenylmethoxy)piperidin-1-yl]-1-[4-(2-methylbutan-2-yl)phenyl]butan-1-one,

www.webofpharma.com

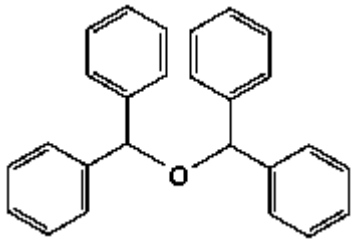
https://thuocngocanh.com/



F. (1*s*,4*s*)-1-[4-(4-*tert*-butylphenyl)-4-oxobutyl]-4-(diphenylmethoxy)piperidine *N*-oxide,



G. (1*r*,4*r*)-1-[4-(4-*tert*-butylphenyl)-4-oxobutyl]-4-(diphenylmethoxy)piperidine *N*-oxide,



H. [oxybis(methanetriyl)]tetrakisbenzene (bis(diphenylmethyl) ether).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

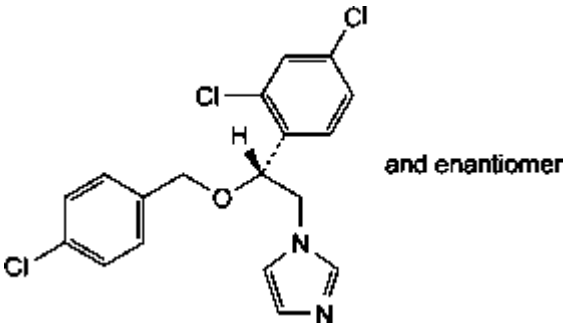
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Econazole

General Notices

(Ph. Eur. monograph 2049)



$C_{18}H_{15}Cl_3N_2O$ 381.7 *27220-47-9*

Action and use

Antifungal.

Ph Eur

DEFINITION

1-[(2*RS*)-2-[(4-Chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Melting point (*2.2.14*): 88 °C to 92 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *econazole CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *econazole for system suitability CRS* (containing impurities A, B and C) in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 25.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, 0.77 g/L solution of *ammonium acetate R* (20:80 *V/V*);

— *mobile phase B*: *methanol R*, *acetonitrile R* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	60 → 10	40 → 90
25 - 27	10	90

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *econazole for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to econazole (retention time = about 15 min): impurity A = about 0.2; impurity B = about 0.6; impurity C = about 1.1.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to econazole.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 75 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 38.17 mg of $C_{18}H_{15}Cl_3N_2O$.

STORAGE

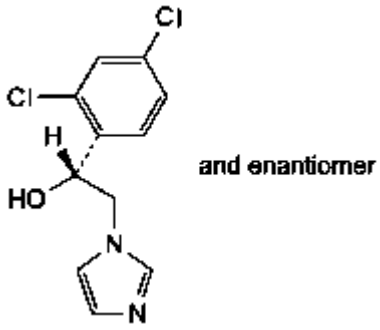
Protected from light.

IMPURITIES

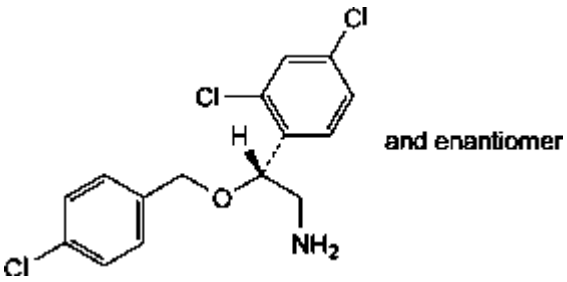
Specified impurities *A, B, C.*

www.webofpharma.com

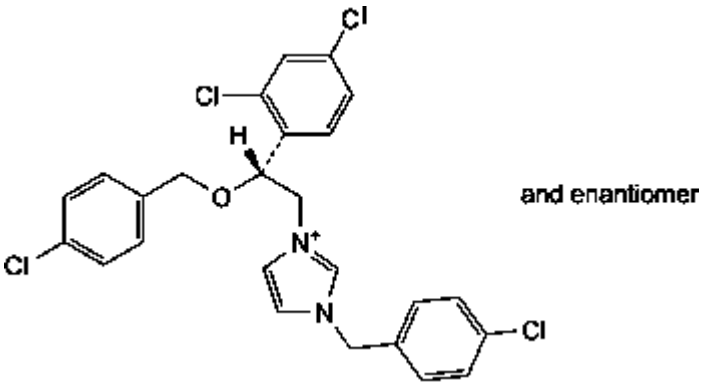
https://thuocngocanh.com/



A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol,



B. (2*RS*)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethanamine,



C. 1-(4-chlorobenzyl)-3-[(2*RS*)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]imidazolium.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Econazole Cream

General Notices

Action and use

Antifungal.

DEFINITION

Econazole Cream contains Econazole Nitrate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of econazole nitrate, $C_{18}H_{15}Cl_3N_2O,HNO_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Mix a quantity of the cream containing 40 mg of Econazole Nitrate with 20 mL of a mixture of 1 volume of 1M *sulfuric acid* and 4 volumes of *methanol* and shake with two 50-mL quantities of *carbon tetrachloride* discarding the organic layers. Make the aqueous phase alkaline with 2M *ammonia* and extract with two 40-mL quantities of *chloroform*. Combine the *chloroform* extracts, shake with 5 g of *anhydrous sodium sulfate*, filter and dilute the filtrate to 100 mL with *chloroform*. Evaporate 50 mL to dryness and dissolve the residue in 50 mL of a mixture of 1 volume of *0.1M hydrochloric acid* and 9 volumes of *propan-2-ol*. The *light absorption* of the resulting solution, Appendix II B, in the range 240 to 350 nm exhibits maxima at 265, 271 and 280 nm. The ratio of the *absorbance* at the maximum at 271 nm to that at the maximum at 280 nm is 1.55 to 1.77. The test is not valid unless the ratio of the *absorbance* in the test for *resolution* is at least 2.

B. In the Assay, the principal peak in the chromatogram obtained with solution (3) has the same retention time as the peak due to econazole in the chromatogram obtained with solution (4).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Buffer Solution

Dissolve 2.5 g of *potassium dihydrogen orthophosphate* and 2.5 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water*.

(1) 0.05% w/v solution of miconazole nitrate in *methanol* (internal standard solution).

(2) Mix a quantity of the cream containing 10 mg of Econazole Nitrate with 20 mL of internal standard solution and 55 mL of *methanol*, warm on a water-bath for 30 seconds, shake for 1 minute, repeat the process twice and add 25 mL of buffer solution. Cool in an ice bath for 15 minutes, centrifuge for 10 minutes and use the supernatant liquid, filtered if necessary.

www.webofpharma.com

https://thuvienthuocngocanh.com/

(3) Prepare in the same manner as solution (2) but using 20 mL of *methanol* in place of internal standard solution.

(4) 10 mL of a 0.1% w/v solution of *econazole nitrate BPCRS* in *methanol* with 20 mL of internal standard solution, 45 mL of *methanol* and 25 mL of buffer solution.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 232 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of buffer solution and 3 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{15}Cl_3N_2O,HNO_3$ in the cream using the declared content of $C_{18}H_{15}Cl_3N_2O,HNO_3$ in *econazole nitrate BPCRS*.

STORAGE

If Econazole Cream is kept in aluminium tubes, their inner surfaces should be coated with a suitable lacquer.

© Crown Copyright 2022

www.webofpharma.com

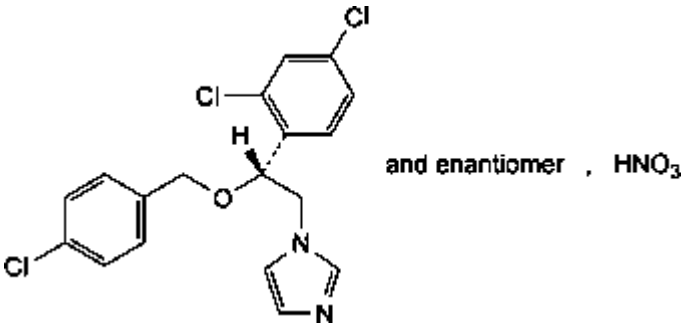
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Econazole Nitrate

General Notices

(Ph. Eur. monograph 0665)



$C_{18}H_{16}Cl_3N_3O_4$ 444.7 *24169-02-6*

Action and use

Antifungal.

Preparations

Econazole Cream

Econazole Pessaries

Ph Eur

DEFINITION

1-[(2*RS*)-2-[(4-Chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole nitrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Very slightly soluble in water, soluble in methanol, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

mp

About 165 °C, with decomposition.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *econazole nitrate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *econazole for system suitability CRS* (containing impurities A, B and C) in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 25.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, 0.77 g/L solution of *ammonium acetate R* (20:80 *V/V*);

— *mobile phase B*: *methanol R*, *acetonitrile R* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	60 → 10	40 → 90
25 - 27	10	90

Flow rate 1.5 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *econazole for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to econazole (retention time = about 15 min): impurity A = about 0.2; impurity B = about 0.6; impurity C = about 1.1.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to econazole.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to the nitrate ion at the beginning of the chromatogram.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 44.47 mg of $C_{18}H_{16}Cl_3N_3O_4$.

STORAGE

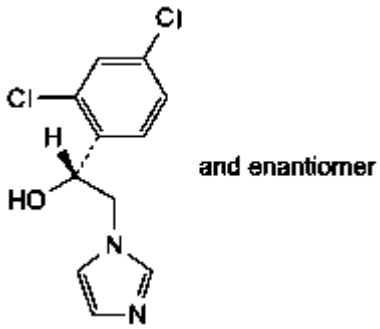
Protected from light.

www.webofpharma.com

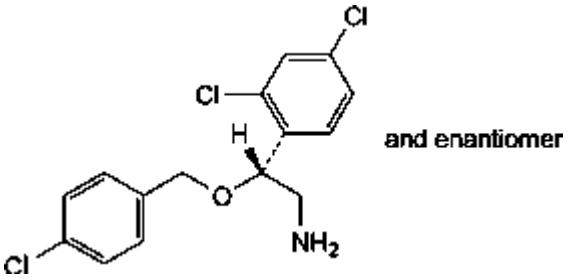
https://thuocngocanh.com/

IMPURITIES

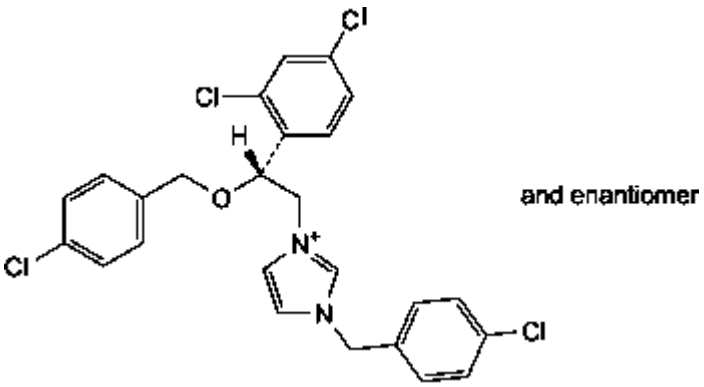
Specified impurities A, B, C.



A. (1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol,



B. (2*RS*)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethanamine,



C. 1-(4-chlorobenzyl)-3-[(2*RS*)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]imidazolium.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Econazole Pessaries

General Notices

Action and use

Antifungal.

DEFINITION

Econazole Pessaries are moulded pessaries containing Econazole Nitrate in a suitable basis.

The pessaries comply with the requirements stated under Vaginal Preparations and with the following requirements.

Content of econazole nitrate, $C_{18}H_{15}Cl_3N_2O,HNO_3$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Mix a quantity of the pessaries, cut into small pieces, containing 40 mg of Econazole Nitrate with 20 mL of a mixture of 1 volume of 1M *sulfuric acid* and 4 volumes of *methanol* and shake with two 50-mL quantities of *hexane*, discarding the organic layers. Make the aqueous phase alkaline with 2M *ammonia* and extract with two 40-mL quantities of *dichloromethane*. Combine the *dichloromethane* extracts, shake with 5 g of *anhydrous sodium sulfate*, filter and dilute the filtrate to 100 mL with *dichloromethane*. Evaporate 50 mL to dryness and dissolve the residue in 50 mL of a mixture of 1 volume of *0.1M hydrochloric acid* and 9 volumes of *propan-2-ol*. The *light absorption* of the resulting solution, Appendix II B, in the range 240 to 350 nm exhibits maxima at 265, 271 and 280 nm. The ratio of the *absorbance* at the maximum at 271 nm to that at the maximum at 280 nm is 1.55 to 1.77. The test is not valid unless the ratio of the *absorbance* in the test for *resolution* is at least 2.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (3).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix a quantity of the pessaries, cut into small pieces, containing 40 mg of Econazole Nitrate with 40 mL of *methanol* and heat under a reflux condenser for 15 minutes. Allow to cool, filter (Whatman No. 1 paper is suitable), wash the filter paper with *methanol* and evaporate the filtrate and washings to a volume of about 5 mL. Filter (Whatman No. 50 paper is suitable), wash the paper with *methanol*, evaporate the filtrate and washings to dryness and dissolve the residue in 2 mL of *methanol*.

(2) Dilute 0.5 mL of solution (1) to 100 mL with *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

(3) 2% w/v of *econazole nitrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and expose to iodine vapour for 1 hour.

MOBILE PHASE

10 volumes of an 85% w/v solution of *formic acid,* 20 volumes of *methanol* and 70 volumes of *dichloromethane*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2). Disregard any spot with an Rf value higher than 0.9.

ASSAY

Dissolve five pessaries in 250 mL of *anhydrous acetic acid* with the aid of gentle heat, allow to cool and carry out Method I for *non-aqueous titration*, Appendix VIII A, using a quantity of the solution containing 0.3 g of Econazole Nitrate and determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 44.47 mg of $C_{18}H_{15}Cl_3N_2O,HNO_3$.

© Crown Copyright 2022

www.webofpharma.com

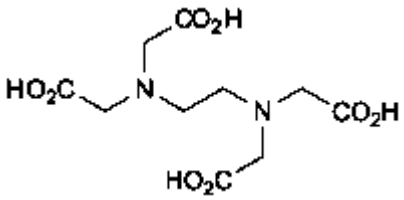
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Edetic Acid

General Notices

(Ph. Eur. monograph 1612)



$C_{10}H_{16}N_2O_8$ 292.2 *60-00-4*

Action and use

Chelating agent.

Ph Eur

DEFINITION

(Ethylenedinitrilo)tetraacetic acid.

Content

98.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water and in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Preparation Discs, after drying the substance to be examined in an oven at 100-105 °C for 2 h.

Comparison *sodium edetate R*, treated as follows: dissolve 0.25 g of *sodium edetate R* in 5 mL of *water R*, add 1.0 mL of *dilute hydrochloric acid R*. Filter, wash the residue with 2 quantities, each of 5 mL, of *water R* and dry the residue in an oven at 100-105 °C for 2 h.

B. To 5 mL of *water R* add 0.1 mL of *ammonium thiocyanate solution R* and 0.1 mL of *ferric chloride solution R1* and mix. The solution is red. Add 0.5 mL of solution S (see Tests). The solution becomes yellowish.

C. To 10 mL of solution S add 0.5 mL of *calcium chloride solution R*. Make alkaline to *red litmus paper R* by the addition of *dilute ammonia R2* and add 3 mL of *ammonium oxalate solution R*. No precipitate is formed.

TESTS

Solution S

Dissolve 5.0 g in 20 mL of *dilute sodium hydroxide solution R* and dilute to 100 mL with *water R*.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Impurity A

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture Dissolve 10.0 g of *ferric sulfate pentahydrate R* in 20 mL of *0.5 M sulfuric acid* and add 780 mL of *water R*. Adjust to pH 2.0 with *1 M sodium hydroxide* and dilute to 1000 mL with *water R*.

Test solution Dissolve 0.100 g of the substance to be examined in 1.0 mL of *1 M sodium hydroxide* and dilute to 25.0 mL with the solvent mixture.

Reference solution Dissolve 40.0 mg of *nitrilotriacetic acid R* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. To 1.0 mL of the solution add 0.1 mL of the test solution and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: *graphitised carbon for chromatography R* (5 µm).

Mobile phase Dissolve 50.0 mg of *ferric sulfate pentahydrate R* in 50 mL of *0.5 M sulfuric acid* and add 750 mL of *water for chromatography R*. Adjust to pH 1.5 with *0.5 M sulfuric acid* or *1 M sodium hydroxide*, add 20 mL of *ethylene glycol R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 273 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL; filter the solutions and inject immediately.

Run time 4 times the retention time of the iron complex of impurity A.

Retention time Iron complex of impurity A = about 5 min; iron complex of edetic acid = about 10 min.

System suitability Reference solution:

— *resolution*: minimum 7.0 between the peaks due to the iron complex of impurity A and the iron complex of edetic acid,

— *signal-to-noise ratio*: minimum 50 for the peak due to impurity A.

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Chlorides (2.4.4)

Maximum 200 ppm.

To 10 mL of solution S add 8 mL of *nitric acid R* and stir for 10 min. A precipitate is formed. Filter and wash the filter with *water R*. Collect the filtrate and the washings and dilute to 20 mL with *water R*. Dilute 10 mL of this solution to 15 mL with *water R*.

Iron (2.4.9)

Maximum 80 ppm.

Dilute 2.5 mL of solution S to 10 mL with *water R* and add 0.25 g of *calcium chloride R* before adding the *thioglycollic acid R*. Allow to stand for 5 min. Also add 0.25 g of *calcium chloride R* to the standard.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 2.0 mL of *dilute sodium hydroxide solution R* and dilute to 300 mL with *water R*. Add 2 g of *hexamethylenetetramine R* and 2 mL of *dilute hydrochloric acid R*. Titrate with *0.1 M zinc sulfate* using about 50 mg of *xylenol orange triturate R* as indicator.

1 mL of *0.1 M zinc sulfate* corresponds to 29.22 mg of $C_{10}H_{16}N_2O_8$.

STORAGE

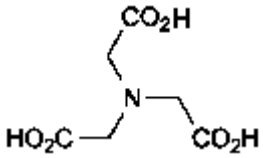
Protected from light.

IMPURITIES

www.webofpharma.com

https://thuocngocanh.com/

Specified impurities *A.*



A. nitrilotriacetic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

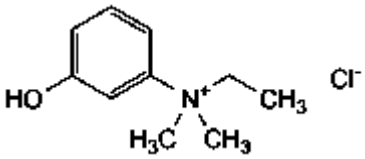
https://thuathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Edrophonium Chloride

General Notices

(Ph. Eur. monograph 2106)



$C_{10}H_{16}ClNO$ 201.7 *116-38-1*

Action and use

Cholinesterase inhibitor.

Preparation

Edrophonium Injection

Ph Eur

DEFINITION

N-Ethyl-3-hydroxy-*N*,*N*-dimethylanilinium chloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *edrophonium chloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.5 g in *water R* and dilute to 25 mL with the same solvent.

pH (*2.2.3*)

4.0 to 5.0.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *3-dimethylaminophenol R* in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Mix 1.0 mL of the test solution and 1.0 mL of reference solution (a) and dilute to 100.0 mL with *water R*. Dilute 10.0 mL of this solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *styrene-divinylbenzene copolymer R* (8-10 µm).

Mobile phase Mix 10 volumes of *acetonitrile R* and 90 volumes of a 7.7 g/L solution of *tetramethylammonium bromide R* previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 281 nm.

Injection 20 µL.

Run time Twice the retention time of edrophonium.

Relative retention With reference to edrophonium (retention time = about 3.8 min): impurity A = about 1.3.

System suitability Reference solution (b):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 2.0 between the peaks due to edrophonium and impurity A.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *any other impurity*: for each impurity, not more than the area of the peak due to edrophonium in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *total*: not more than 5 times the area of the peak due to edrophonium in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *disregard limit*: 0.5 times the area of the peak due to edrophonium in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator at a pressure not exceeding 0.7 kPa for 24 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 8.3 IU/mg.

ASSAY

Dissolve 0.150 g in 60 mL of a mixture of equal volumes of *acetic anhydride R* and *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 20.17 mg of $C_{10}H_{16}ClNO$.

STORAGE

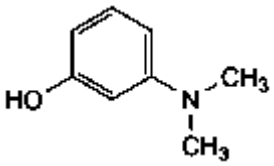
Protected from light.

IMPURITIES

Specified impurities A.

www.webofpharma.com

https://thuocngocanh.com/



A. 3-(dimethylamino)phenol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Edrophonium Injection

General Notices

Action and use

Cholinesterase inhibitor.

DEFINITION

Edrophonium Injection is a sterile solution of Edrophonium Chloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of edrophonium chloride, $C_{10}H_{16}ClNO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a sufficient volume of the injection with 0.1M *sodium hydroxide* to give a solution containing 0.001% w/v of Edrophonium Chloride. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 350 nm exhibits two maxima, at 240 nm and 294 nm. The *absorbances* at the maxima are about 1.1 and about 0.34 respectively.

B. To a volume containing 20 mg of Edrophonium Chloride add 0.05 mL of *iron(III) chloride solution R1*. A reddish violet colour is produced.

C. Yields reaction A characteristic *of chlorides*, Appendix VI.

TESTS

Acidity

pH, 5.0 to 6.0, Appendix V L.

Dimethylaminophenol

To a volume containing 50 mg of Edrophonium Chloride add 10 mL of *phosphate buffer pH 8.0* and extract with two 20 mL quantities of *chloroform*. Wash the extracts successively with two 10 mL quantities of *water*, extract with 10 mL of 0.1M *sodium hydroxide* and discard the chloroform. The *absorbance* of the resulting solution at 293 nm is not more than 0.125, Appendix II B.

ASSAY

To a volume containing 50 mg of Edrophonium Chloride add sufficient *water* to produce 100 mL. Dilute 10 mL of this solution to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 273 nm, Appendix II B. Calculate the content of

www.webofpharma.com

https://thuocngocanh.com/

$C_{10}H_{16}ClNO$ taking 110 as the value of *A* (1%, 1 cm) at the maximum at 273 nm.

STORAGE

Edrophonium Injection should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Egg Phospholipids for Injection

General Notices

(Ph. Eur. monograph 2315)

Egg lecithins *93685-90-6*

Egg phosphatidylcholines *97281-44-2*

Ph Eur

DEFINITION

Mixture of natural phospholipids of egg yolk, and fractions thereof, for injection. A suitable stabiliser such as α-tocopherol may be added.

Content

— *phosphatidylcholine*: minimum 60.0 per cent (anhydrous substance);

— *phosphatidylethanolamine*: maximum 20.0 per cent (anhydrous substance);

— *lysophosphatidylcholine*: maximum 3.0 per cent (anhydrous substance).

PRODUCTION

Viral safety

The requirements of general chapter *5.1.7* apply.

CHARACTERS

Appearance

Almost white or yellow mass or powder.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent) and freely soluble in heptane.

IDENTIFICATION

Carry out either test A or test B. If sphingomyelin is not detected with test A or B, carry out test C.

A. Thin-layer chromatography (*2.2.27*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *phosphatidylethanolamine from egg yolk CRS* in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dissolve 15 mg of *lysophosphatidylcholine from egg yolk CRS* and 15 mg of *sphingomyelin from egg yolk R* in *methanol R* and dilute to 20.0 mL with the same solvent.

Reference solution (c) Dissolve 15 mg of *phosphatidylcholine from egg yolk CRS* in *methanol R*, add 5 mL of reference solution (a) and 1 mL of reference solution (b) and dilute to 50.0 mL with *methanol R*.

Plate *TLC silica gel plate R* (2-10 µm).

Mobile phase *water R*, *methanol R*, *chloroform R* (4:25:65 *V/V/V*).

Application 4 µL of the test solution and reference solution (c), as slim bands.

Development Over 2/3 of the plate.

Detection Spray with *copper sulfate solution R1* and heat at 170 °C for 5-15 min; the phospholipids appear as brownish-grey bands.

Retardation factors Lysophosphatidylcholine = about 0.15; sphingomyelin = about 0.2; phosphatidylcholine = about 0.3; phosphatidylethanolamine = about 0.6.

System suitability Reference solution (c):

— the chromatogram shows 4 clearly separated bands.

Results:

— the principal band in the chromatogram obtained with the test solution is similar in position and colour to the band due to phosphatidylcholine in the chromatogram obtained with reference solution (c);

— the band due to sphingomyelin is visible in the chromatogram obtained with the test solution.

B. Liquid chromatography (*2.2.29*) as described in the assay with the following modifications.

Injection Test solution and reference solution (h).

Identification of peaks Use the chromatogram obtained with reference solution (h) to identify the peak due to sphingomyelin.

Relative retention With reference to phosphatidylcholine (retention time = about 8 min): sphingomyelin = about 1.1 (may be eluted as 1 or 2 peaks).

Results:

— the principal peak in the chromatogram obtained with the test solution is due to phosphatidylcholine;

— the peak due to sphingomyelin in the chromatogram obtained with the test solution has a signal-to-noise ratio not less than 3.

www.webofpharma.com

https://thuocngocanh.com/

C. Composition of fatty acids (*2.4.22, Method B*). Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the substance:

— the oleic acid (C18:1) content is greater than that of linoleic acid (C18:2);

— arachidonic acid (C20:4) and docosahexaenoic acid (C22:6) are present.

TESTS

Acid value (*2.5.1*)

Maximum 20.

Dissolve 2.00 g in 50 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *ether R*, previously neutralised with *0.1 M potassium hydroxide* using 0.5 mL of *phenolphthalein solution R1* as indicator.

Peroxide value (*2.5.5, Method A*)

Maximum 3.

Titrate with *0.01 M sodium thiosulfate*, determining the end-point potentiometrically (*2.2.20*).

Nonphosphatidyl lipids

Maximum 7.0 per cent.

Test solution Dissolve 0.500 g of the substance to be examined in *ether R* and dilute to 15.0 mL with the same solvent.

Chromatography column *l* = 0.35-0.4 m, Ø = 10-20 mm.

Preparation of the column Transfer 1 kg of silica gel with a particle size of 0.05-0.2 mm into a container fitted with a screw cap. Add 150 g of *water R*, shake thoroughly, and allow to stand for 24 h. Suspend 15 g of the prepared adsorbent in 50 mL of *ether R* and introduce into the column. Allow the *ether R* to pass through the column to a level of about 1 cm above the silica gel bed.

Transfer the test solution to the column. Rinse with 2 quantities, each of 15 mL, of *ether R*, allowing each to pass through the column before adding the next. After rinsing, elute with 105 mL of *ether R*. Combine the rinsings and eluate and evaporate to dryness. Remove any volatile components with a stream of nitrogen and dry the residue at 105 °C for 20 min.

Calculate the percentage content of nonphosphatidyl lipids using the following expression:

$$\frac{m_1}{m_2} \times 100$$

m_1 = mass of the residue, in milligrams;

m_2 = mass of the substance to be examined in the test solution, in milligrams.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.500-1.00 g.

www.webofpharma.com

https://nhathuocngocanh.com/

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

Absence of *Escherichia coli* (2.6.13).

Absence of *Salmonella* (2.6.13).

Bacterial endotoxins (2.6.14, Method A)

Less than 6 IU/g. The suitability of the method must be verified and a risk assessment must be carried out according to general chapter 5.1.10. *Guidelines for using the test for bacterial endotoxins* since the phospholipids can interfere with the test.

ASSAY

Liquid chromatography (2.2.29).

Solvent mixture Mix 8 volumes of *water R* and 46 volumes of *2-propanol R*, then add 46 volumes of *hexane R*.

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

NOTE: if saturation of the peak due to phosphatidylcholine is observed, the test solution may be diluted with the solvent mixture to quantify this compound.

Reference solution (a_1) Dissolve 60 mg of *phosphatidylcholine from egg yolk CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solutions (b_1), (c_1), (d_1), (e_1), (f_1) Dilute reference solution (a_1) with the solvent mixture to obtain 5 reference solutions, the concentrations of which span 60 per cent to 140 per cent of the expected content of phosphatidylcholine in the test solution.

Reference solution (a_2) Dissolve 40 mg of *phosphatidylethanolamine from egg yolk CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solutions (b_2), (c_2), (d_2), (e_2), (f_2) Dilute reference solution (a_2) with the solvent mixture to obtain 5 reference solutions, the concentrations of which span 60 per cent to 140 per cent of the expected content of phosphatidylethanolamine in the test solution.

Reference solution (a_3) Dissolve 40 mg of *lysophosphatidylcholine from egg yolk CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solutions (b_3), (c_3), (d_3), (e_3), (f_3) Dilute reference solution (a_3) with the solvent mixture to obtain 5 reference solutions, the concentrations of which span 60 per cent to 140 per cent of the expected content of lysophosphatidylcholine in the test solution.

Reference solution (g) Mix 5 mL of reference solution (a_1) and 5 mL of reference solution (a_2).

Reference solution (h) Dissolve 5 mg of *sphingomyelin from egg yolk R* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *diol silica gel for chromatography R* (5 µm);

— *temperature*: 55 °C.

Mobile phase:

— *mobile phase A*: mix 0.08 volumes of *triethylamine R*, 1.5 volumes of *glacial acetic acid R*, 17 volumes of *2-propanol R* and 81.42 volumes of *hexane R*;

— *mobile phase B*: mix 0.08 volumes of *triethylamine R*, 1.5 volumes of *glacial acetic acid R*, 14 volumes of *water for chromatography R* and 84.42 volumes of *2-propanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.0	95	5
2.0 - 7.0	95 → 80	5 → 20
7.0 - 10.5	80 → 60	20 → 40
10.5 - 17.0	60 → 0	40 → 100
17.0 - 19.5	0	100

Flow rate 1.0 mL/min.

Detection Evaporative light-scattering detector; the following settings have been found to be suitable; if the detector has different setting parameters, adjust the detector settings so as to comply with the system suitability criteria:

— *carrier gas*: *nitrogen R*;

— *flow rate*: 2.5 mL/min;

— *evaporator temperature*: 50 °C.

Injection 20 µL of the test solution and reference solutions ($b_{1,2,3}$), ($c_{1,2,3}$), ($d_{1,2,3}$), ($e_{1,2,3}$), ($f_{1,2,3}$) and (g).

Identification of peaks Use the chromatograms obtained with reference solutions (f_1), (f_2) and (f_3) to identify the peaks due to phosphatidylcholine, phosphatidylethanolamine and lysophosphatidylcholine.

Relative retention With reference to phosphatidylcholine (retention time = about 8 min): phosphatidylethanolamine = about 0.8; lysophosphatidylcholine = about 1.2 (may be eluted as 1 or 2 peaks).

www.webofpharma.com

https://thuocngocanh.com/

Establish calibration curves with the logarithm of the concentration of phosphatidylcholine, phosphatidylethanolamine and lysophosphatidylcholine in reference solutions ($b_{1,2,3}$), ($c_{1,2,3}$), ($d_{1,2,3}$), ($e_{1,2,3}$) and ($f_{1,2,3}$) as the abscissa and the logarithm of the corresponding peak areas as the ordinate.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to phosphatidylethanolamine and phosphatidylcholine in the chromatogram obtained with reference solution (g);

— *phosphatidylcholine*:

— *repeatability*: maximum relative standard deviation of 5.0 per cent determined on 6 injections of reference solution (f_1);

— *correlation coefficient*: minimum 0.995;

— *phosphatidylethanolamine*:

— *repeatability*: maximum relative standard deviation of 5.0 per cent determined on 6 injections of reference solution (f_2);

— *correlation coefficient*: minimum 0.995;

— *lysophosphatidylcholine*:

— *repeatability*: maximum relative standard deviation of 5.0 per cent determined on 6 injections of reference solution (f_3);

— *correlation coefficient*: minimum 0.99.

Calculate the percentage contents of phosphatidylcholine, phosphatidylethanolamine and lysophosphatidylcholine using the calibration curves.

STORAGE

Under nitrogen, protected from light, at -15 °C or below.

LABELLING

The label states:

— the specified content range of phosphatidylcholine;

— the specified content range of phosphatidylethanolamine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

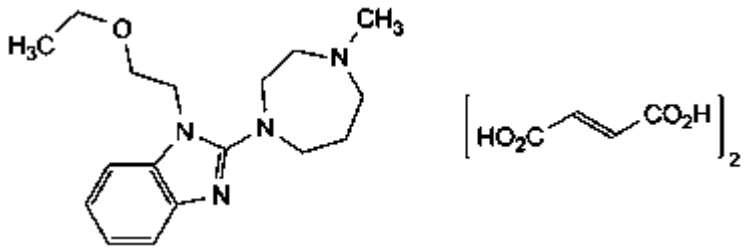
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Emedastine Fumarate

General Notices

(Emedastine Difumarate, Ph. Eur. monograph 2242)



$C_{25}H_{34}N_4O_9$ 534.6 *87233-62-3*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Ph Eur

DEFINITION

1-(2-Ethoxyethyl)-2-(4-methylhexahydro-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole bis[hydrogen (2*E*)-butenedioate].

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish powder.

Solubility

Soluble in water, sparingly soluble in anhydrous ethanol, very slightly soluble in acetone.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *emedastine difumarate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 2.50 g in *water R* and dilute to 50 mL with the same solvent.

pH (*2.2.3*)

3.0 to 4.5.

Dissolve 0.20 g in 100 mL of *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *emedastine impurity E CRS* in the mobile phase and dilute to 25 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of the substance to be examined in the mobile phase. Add 0.5 mL of reference solution (a) and dilute to 10 mL with the mobile phase.

Reference solution (c) Dilute 5.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 3.9 g of *disodium hydrogen phosphate dodecahydrate R* and 2.5 g of *sodium dodecyl sulfate R* in *water R* and dilute to 1000.0 mL with the same solvent. Adjust to pH 2.4 with *phosphoric acid R*. Mix 550 volumes of this solution with 450 volumes of *acetonitrile R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

www.webofpharma.com

https://thuocngocanh.com/

Run time Twice the retention time of emedastine.

Relative retention With reference to emedastine (retention time = about 18 min): fumaric acid = about 0.1; impurity A = about 0.2; impurity B = about 0.3; impurity C = about 0.5; impurity D = about 0.7; impurity E = about 0.9; impurity F = about 1.4.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to emedastine.

Limits:

— *impurities A, B, C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard the peak due to fumaric acid.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 26.73 mg of $C_{25}H_{34}N_4O_9$.

STORAGE

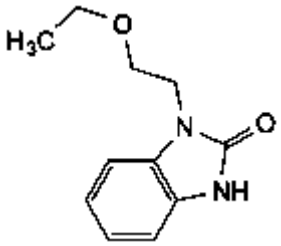
Protected from light.

IMPURITIES

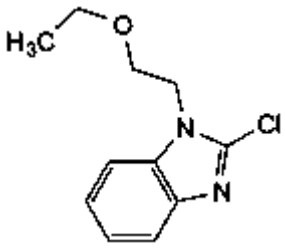
Specified impurities *A, B, C, D, E, F*.

www.webofpharma.com

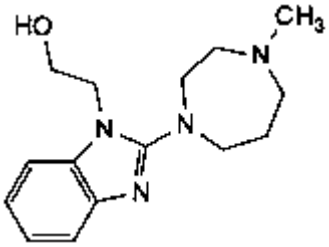
https://thuathuocngocanh.com/



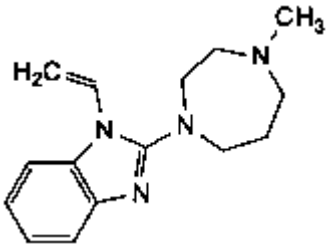
A. 1-(2-ethoxyethyl)-1,3-dihydro-2*H*-benzimidazol-2-one,



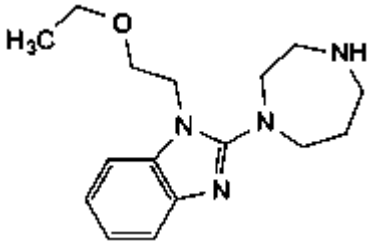
B. 2-chloro-1-(2-ethoxyethyl)-1*H*-benzimidazole,



C. 2-[2-(4-methylhexahydro-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazol-1-yl]ethanol,



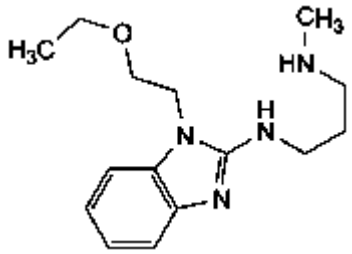
D. 1-ethenyl-2-(4-methylhexahydro-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole,



E. 1-(2-ethoxyethyl)-2-(hexahydro-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole,

www.webofpharma.com

https://thuvienthuocngocanh.com/



F. *N*-[1-(2-ethoxyethyl)-1*H*-benzimidazol-2-yl]-*N'*-methylpropane-1,3-diamine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Emulsifying Cetostearyl Alcohol (Type A)

General Notices

(Ph. Eur. monograph 0801)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of cetostearyl alcohol and sodium cetostearyl sulfate. A suitable buffer may be added.

Content

— *cetostearyl alcohol*: minimum 80.0 per cent (anhydrous substance);

— *sodium cetostearyl sulfate*: minimum 7.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow, waxy mass, plates, flakes or granules.

Solubility

Soluble in hot water giving an opalescent solution, practically insoluble in cold water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, C, D.

Second identification: A, C, D.

A. Thin-layer chromatography (*2.2.27*).

Test solution (a) Dissolve 0.1 g of the substance to be examined in 10 mL of *trimethylpentane R*, heating on a water-bath. Shake with 2 mL of *ethanol (70 per cent V/V) R* and allow to separate. Use the lower layer as test solution (b). Dilute 1 mL of the upper layer to 8 mL with *trimethylpentane R*.

Test solution (b) Use the lower layer obtained in the preparation of test solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 24 mg of *cetyl alcohol CRS* and 16 mg of *stearyl alcohol CRS* in 10 mL of *trimethylpentane R*.

Reference solution (b) Dissolve 20 mg of *sodium cetostearyl sulfate R* in 10 mL of *ethanol (70 per cent V/V) R*, heating on a water-bath.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *water R*, *acetone R*, *methanol R* (20:40:40 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 50 g/L solution of *phosphomolybdic acid R* in *ethanol (96 per cent) R*; heat at 120 °C until spots appear (about 5 min).

Results:

— the 2 principal spots in the chromatogram obtained with test solution (a) are similar in position and colour to the principal spots in the chromatogram obtained with reference solution (a);

— 2 of the spots in the chromatogram obtained with test solution (b) are similar in position and colour to the principal spots in the chromatogram obtained with reference solution (b).

B. Examine the chromatograms obtained in the assay of cetostearyl alcohol.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the 2 principal peaks in the chromatograms obtained with reference solutions (a) and (b).

C. It gives a yellow colour to a non-luminous flame.

D. To 0.3 g add 20 mL of *anhydrous ethanol R* and heat to boiling on a water-bath with shaking. Filter the mixture immediately, evaporate to dryness and take up the residue in 7 mL of *water R*. To 1 mL of the solution add 0.1 mL of a 1 g/L solution of *methylene blue R*, 2 mL of *dilute sulfuric acid R* and 2 mL of *methylene chloride R* and shake. A blue colour develops in the lower layer.

TESTS

Acid value (*2.5.1*)

Maximum 2.0.

Iodine value (*2.5.4, Method A*)

Maximum 3.0.

Dissolve 2.00 g in 25 mL of *methylene chloride R*.

Saponification value (*2.5.6*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 2.0.

Water (2.5.12)

Maximum 3.0 per cent, determined on 2.50 g.

ASSAY

Cetostearyl alcohol

Gas chromatography (2.2.28).

Internal standard solution Dissolve 0.200 g of *1-nonadecanol CRS* in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent.

Test solution Dissolve 0.200 g of the substance to be examined in 25.0 mL of the internal standard solution. Add 25 mL of *water R* and shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers. Combine the upper layers, wash with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Reference solution (a) Dissolve 0.100 g of *cetyl alcohol CRS* in 25.0 mL of the internal standard solution. Add 25 mL of *water R* and shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers. Combine the upper layers, wash with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Reference solution (b) Dissolve 0.100 g of *stearyl alcohol CRS* in 25.0 mL of the internal standard solution. Add 25 mL of *water R* and shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers. Combine the upper layers, wash with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 20	150 → 250
Injection port		250

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Elution order Cetyl alcohol, stearyl alcohol, 1-nonadecanol.

Calculate the percentage content of cetyl alcohol in the substance to be examined using the following expression and taking into account the assigned content of *cetyl alcohol CRS*:

$$A_x \times \frac{A_2}{A_1} \times \frac{m_{x,y}}{A_{x,y}} \times \frac{1}{m} \times 100$$

A_x = area of the peak due to cetyl alcohol in the chromatogram obtained with the test solution;

$A_{x,y}$ = area of the peak due to *cetyl alcohol CRS* in the chromatogram obtained with reference solution (a);

A_1 = area of the peak due to the internal standard in the chromatogram obtained with the test solution;

A_2 = area of the peak due to the internal standard in the chromatogram obtained with reference solution (a);

m = mass of the substance to be examined in the test solution, in milligrams;

$m_{x,y}$ = mass of *cetyl alcohol CRS* in reference solution (a), in milligrams.

Calculate the percentage content of stearyl alcohol in the substance to be examined using the following expression and taking into account the assigned content of *stearyl alcohol CRS*:

$$A_z \times \frac{A_3}{A_1} \times \frac{m_{z,y}}{A_{z,y}} \times \frac{1}{m} \times 100$$

A_z = area of the peak due to stearyl alcohol in the chromatogram obtained with the test solution;

$A_{z,y}$ = area of the peak due to *stearyl alcohol CRS* in the chromatogram obtained with reference solution (b);

A_1 = area of the peak due to the internal standard in the chromatogram obtained with the test solution;

A_3 = area of the peak due to the internal standard in the chromatogram obtained with reference solution (b);

m = mass of the substance to be examined in the test solution, in milligrams;

$m_{z,y}$ = mass of *stearyl alcohol CRS* in reference solution (b), in milligrams.

The percentage content of cetostearyl alcohol corresponds to the sum of the percentage contents of cetyl alcohol and stearyl alcohol.

Sodium cetostearyl sulfate

www.webofpharma.com

https://thuocngocanh.com/

Disperse 0.300 g in 25 mL of *methylene chloride R*. Add 50 mL of *water R* and 10 mL of *dimidium bromide-sulfan blue mixed solution R*. Titrate with *0.004 M benzethonium chloride*, using sonication, heating, and allowing the layers to separate before each addition, until the colour of the lower layer changes from pink to grey.

1 mL of *0.004 M benzethonium chloride* is equivalent to 1.434 mg of sodium cetostearyl sulfate.

LABELLING

The label states, where applicable, the name and concentration of any added buffer.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Emulsifying Cetostearyl Alcohol (Type B)

General Notices

(Ph. Eur. monograph 0802)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of cetostearyl alcohol and sodium laurilsulfate. A suitable buffer may be added.

Content

— *cetostearyl alcohol*: minimum 80.0 per cent (anhydrous substance);

— *sodium laurilsulfate*: minimum 7.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or pale yellow, waxy mass, plates, flakes or granules.

Solubility

Soluble in hot water giving an opalescent solution, practically insoluble in cold water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, C, D.

Second identification: A, C, D.

A. Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.1 g of the substance to be examined in 10 mL of *trimethylpentane R*, heating on a water-bath. Shake with 2 mL of *ethanol (70 per cent V/V) R* and allow to separate. Use the lower layer as test solution (b). Dilute 1 mL of the upper layer to 8 mL with *trimethylpentane R*.

Test solution (b) Use the lower layer obtained in the preparation of test solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 24 mg of *cetyl alcohol CRS* and 16 mg of *stearyl alcohol CRS* in 10 mL of *trimethylpentane R*.

Reference solution (b) Dissolve 20 mg of *sodium laurilsulfate CRS* in 10 mL of *ethanol (70 per cent V/V) R*, heating on a water-bath.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *water R*, *acetone R*, *methanol R* (20:40:40 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a 50 g/L solution of *phosphomolybdic acid R* in *ethanol (96 per cent) R*; heat at 120 °C until spots appear (about 5 min).

Results:

— the 2 principal spots in the chromatogram obtained with test solution (a) are similar in position and colour to the principal spots in the chromatogram obtained with reference solution (a);

— 1 of the spots in the chromatogram obtained with test solution (b) is similar in position and colour to the principal spot in the chromatogram obtained with reference solution (b).

B. Examine the chromatograms obtained in the assay of cetostearyl alcohol.

Results The 2 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the 2 principal peaks in the chromatograms obtained with reference solutions (a) and (b).

C. It gives a yellow colour to a non-luminous flame.

D. To 0.3 g add 20 mL of *anhydrous ethanol R* and heat to boiling on a water-bath with shaking. Filter the mixture immediately, evaporate to dryness and take up the residue in 7 mL of *water R*. To 1 mL of the solution add 0.1 mL of a 1 g/L solution of *methylene blue R*, 2 mL of *dilute sulfuric acid R* and 2 mL of *methylene chloride R* and shake. A blue colour develops in the lower layer.

TESTS

Acid value (*2.5.1*)

Maximum 2.0.

Iodine value (*2.5.4, Method A*)

Maximum 3.0.

Dissolve 2.00 g in 25 mL of *methylene chloride R*.

Saponification value (*2.5.6*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 2.0.

Water (2.5.12)

Maximum 3.0 per cent, determined on 2.50 g.

ASSAY

Cetostearyl alcohol

Gas chromatography (2.2.28).

Internal standard solution Dissolve 0.200 g of *1-nonadecanol CRS* in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent.

Test solution Dissolve 0.200 g of the substance to be examined in 25.0 mL of the internal standard solution. Add 25 mL of *water R* and shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers. Combine the upper layers, wash with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Reference solution (a) Dissolve 0.100 g of *cetyl alcohol CRS* in 25.0 mL of the internal standard solution. Add 25 mL of *water R* and shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers. Combine the upper layers, wash with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Reference solution (b) Dissolve 0.100 g of *stearyl alcohol CRS* in 25.0 mL of the internal standard solution. Add 25 mL of *water R* and shake with 4 quantities, each of 25 mL, of *pentane R*, adding *sodium chloride R*, if necessary, to facilitate the separation of the layers. Combine the upper layers, wash with 2 quantities, each of 30 mL, of *water R*, dry over *anhydrous sodium sulfate R* and filter.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 20	150 → 250
Injection port		250

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Elution order Cetyl alcohol, stearyl alcohol, 1-nonadecanol.

Calculate the percentage content of cetyl alcohol in the substance to be examined using the following expression and taking into account the assigned content of *cetyl alcohol CRS*:

$$A_x \times \frac{A_2}{A_1} \times \frac{m_{x,y}}{A_{x,y}} \times \frac{1}{m} \times 100$$

A_x = area of the peak due to cetyl alcohol in the chromatogram obtained with the test solution;

$A_{x,y}$ = area of the peak due to *cetyl alcohol CRS* in the chromatogram obtained with reference solution (a);

A_1 = area of the peak due to the internal standard in the chromatogram obtained with the test solution;

A_2 = area of the peak due to the internal standard in the chromatogram obtained with reference solution (a);

m = mass of the substance to be examined in the test solution, in milligrams;

$m_{x,y}$ = mass of *cetyl alcohol CRS* in reference solution (a), in milligrams.

Calculate the percentage content of stearyl alcohol in the substance to be examined using the following expression and taking into account the assigned content of *stearyl alcohol CRS*:

$$A_z \times \frac{A_3}{A_1} \times \frac{m_{z,y}}{A_{z,y}} \times \frac{1}{m} \times 100$$

A_z = area of the peak due to stearyl alcohol in the chromatogram obtained with the test solution;

$A_{z,y}$ = area of the peak due to *stearyl alcohol CRS* in the chromatogram obtained with reference solution (b);

A_1 = area of the peak due to the internal standard in the chromatogram obtained with the test solution;

A_3 = area of the peak due to the internal standard in the chromatogram obtained with reference solution (b);

m = mass of the substance to be examined in the test solution, in milligrams;

$m_{z,y}$ = mass of *stearyl alcohol CRS* in reference solution (b), in milligrams.

The percentage content of cetostearyl alcohol corresponds to the sum of the percentage contents of cetyl alcohol and stearyl alcohol.

Sodium laurilsulfate

www.webofpharma.com

https://thuocngocanh.com/

Disperse 0.300 g in 25 mL of *methylene chloride R*. Add 50 mL of *water R* and 10 mL of *dimidium bromide-sulfan blue mixed solution R*. Titrate with *0.004 M benzethonium chloride*, using sonication, heating, and allowing the layers to separate before each addition, until the colour of the lower layer changes from pink to grey.

1 mL of *0.004 M benzethonium chloride* is equivalent to 1.154 mg of sodium laurilsulfate.

LABELLING

The label states, where applicable, the name and concentration of any added buffer.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Emulsifying Ointment

General Notices

DEFINITION

Emulsifying Wax	300 g
White Soft Paraffin	500 g
Liquid Paraffin	200 g

Extemporaneous preparation

The following directions apply.

Melt together and stir until cold.

The ointment complies with the requirements stated under Topical Semi-solid Preparations.

© Crown Copyright 2022

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Emulsifying Wax

General Notices

Anionic Emulsifying Wax

DEFINITION

Emulsifying Wax contains Cetostearyl Alcohol and either Sodium Lauryl Sulfate or sodium salts of similar sulfated higher primary aliphatic alcohols.

Extemporaneous preparation

The following formula and directions apply.

Cetostearyl Alcohol	90 g
Sodium Lauryl Sulfate	10 g
Purified Water	4 mL

Melt the Cetostearyl Alcohol and heat to about 95°. Add the Sodium Lauryl Sulfate, mix, add the Purified Water, heat to 115° and maintain at this temperature, stirring vigorously, until frothing ceases and the product is translucent. Cool quickly.

CHARACTERISTICS

An almost white or pale yellow, waxy solid or flakes, becoming plastic when warmed.

Practically insoluble in *water*, forming an emulsion; partly soluble in *ethanol (96%)*.

IDENTIFICATION

A. *Melting point* of the residue obtained in the test for Unsaponifiable matter, about 52°, Appendix V A.

B. Complies with the test for sulfated ash.

TESTS

Acidity

To 20 g add a mixture of 40 mL of *ether* and 75 mL of *ethanol (96%)* previously neutralised to *phenolphthalein solution R1* and warm gently until solution is effected. Titrate with *0.1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator until a pink colour which persists for at least 15 seconds is obtained. Not more than 1.0 mL of *0.1M sodium hydroxide VS* is required.

Alkalinity

www.webofpharma.com

https://thuocngocanh.com/

Disperse 5.0 g in 25 mL of warm *ethanol (96%)* previously neutralised to *phenolphthalein solution R1* and cool. No colour is produced on the addition of 0.5 mL of *phenolphthalein solution R1*.

Alcohols

To 3.5 g of the residue obtained in the test for Unsaponifiable matter add 12 g of *stearic anhydride* and 10 mL of *xylene* and heat gently under a reflux condenser for 30 minutes. Cool, add a mixture of 40 mL of *pyridine* and 4 mL of *water*, heat under a reflux condenser for a further 30 minutes and titrate the hot solution with *1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Repeat the operation without the residue. The difference between the titrations is 12.8 to 14.2 mL.

Iodine value

Not more than 3.0 *(iodine monochloride method)*, Appendix X E.

Saponification value

Not more than 2.0, Appendix X G. Use 20 g.

Sodium alkyl sulfates

Not less than 8.7%, calculated as $C_{12}H_{25}O_4SNa$ with reference to the anhydrous substance, when determined by the following method. Dissolve 0.25 g as completely as possible in 15 mL of *chloroform*, add 30 mL of *water*, 10 mL of 1M *sulfuric acid* and 1 mL of *dimethyl yellow and oracet blue 2R solution* and titrate with 0.004M *benzethonium chloride VS*, shaking vigorously and allowing the layers to separate after each addition, until the chloroform layer acquires a permanent clear green colour. Each mL of 0.004M *benzethonium chloride VS* is equivalent to 1.154 mg of $C_{12}H_{25}O_4SNa$.

Sulfated ash

Not more than 3.0%, Appendix IX A.

Unsaponifiable matter

Not less than 86.0%, calculated with reference to the anhydrous substance, Appendix X H. Use 5 g and omit the titration of the residue.

Water

Not more than 4.0% w/w, Appendix IX C. Use 0.6 g.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

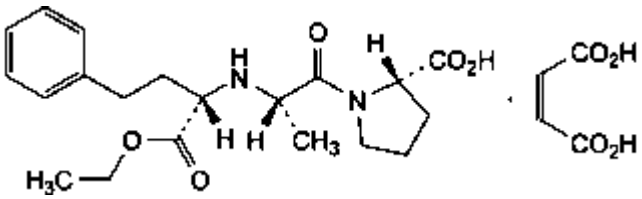
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Enalapril Maleate

General Notices

(Ph. Eur. monograph 1420)



$C_{24}H_{32}N_2O_9$ 492.5 *76095-16-4*

Action and use

Angiotensin converting enzyme inhibitor.

Preparation

Enalapril Tablets

Ph Eur

DEFINITION

(2*S*)-1-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid hydrogen (*Z*)-butenedioate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in methanol, practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

www.webofpharma.com

https://nhathuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison enalapril maleate CRS.

TESTS

Solution S

Dissolve 0.25 g in carbon dioxide-free water R and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

pH (2.2.3)

2.4 to 2.9 for solution S.

Specific optical rotation (2.2.7)

-51 to -48 (dried substance), determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Buffer solution A Dissolve 2.8 g of sodium dihydrogen phosphate monohydrate R in 950 mL of water for chromatography R, adjust to pH 2.5 with phosphoric acid R and dilute to 1000 mL with water for chromatography R.

Buffer solution B Dissolve 2.8 g of sodium dihydrogen phosphate monohydrate R in 950 mL of water for chromatography R, adjust to pH 6.8 with strong sodium hydroxide solution R and dilute to 1000 mL with water for chromatography R.

Solvent mixture acetonitrile R1, buffer solution A (5:95 *V/V*).

Test solution (a) Dissolve 30 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Test solution (b) Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 3 mg of enalapril for system suitability CRS (containing impurity A) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of enalapril impurity mixture A CRS (impurities C and H) in 1.0 mL of the solvent mixture.

Reference solution (d) Dissolve 2.0 mg of enalapril impurity G CRS in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 20.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.15 m, Ø = 4.1 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm);

— *temperature*: 70 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, buffer solution B (5:95 *V/V*);

— *mobile phase B*: buffer solution B, *acetonitrile R1* (34:66 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	95	5
3 - 23	95 → 40	5 → 60
23 - 30	40	60

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 50 µL of test solution (a) and reference solutions (a), (b) and (c); for impurity G, test solution (b) and reference solution (d).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram supplied with *enalapril impurity mixture A CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C and H; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity G.

Relative retention With reference to enalapril (retention time = about 13 min): maleic acid = about 0.1; impurity C = about 0.2; impurity A = about 1.1; impurity G = about 1.2; impurity H = about 1.3.

System suitability:

— *signal-to-noise ratio*: minimum 40 for the peak due to enalapril in the chromatogram obtained with reference solution (a); minimum 40 for the peak due to impurity G in the chromatogram obtained with reference solution (d);

— *peak-to-valley ratio*: minimum 10, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to enalapril in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity H by 2.0;

www.webofpharma.com

https://thuocngocanh.com/

— for impurity G, use the concentration of impurity G in reference solution (d);

— for impurities other than G, use the concentration of enalapril maleate in reference solution (a).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity H*: maximum 0.3 per cent;

— *impurities C, G*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to maleic acid.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). Titrate to the 2nd point of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 16.42 mg of $C_{24}H_{32}N_2O_9$.

STORAGE

Protected from light.

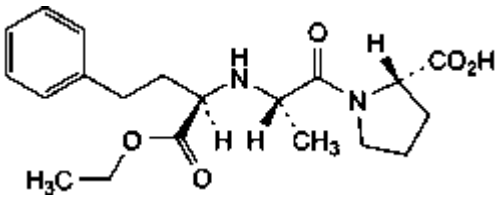
IMPURITIES

Specified impurities A, C, G, H.

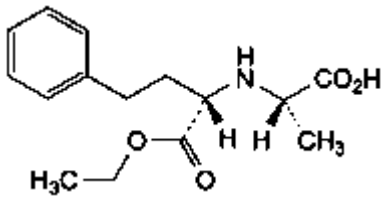
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, D, E, F, I.

www.webofpharma.com

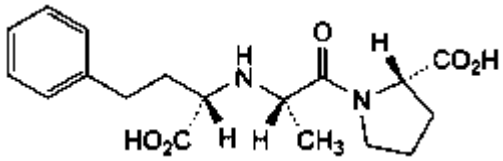
https://thuocngocanh.com/



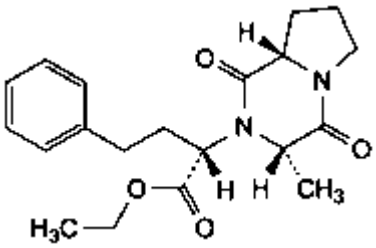
A. (2*S*)-1-[(2*S*)-2-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid,



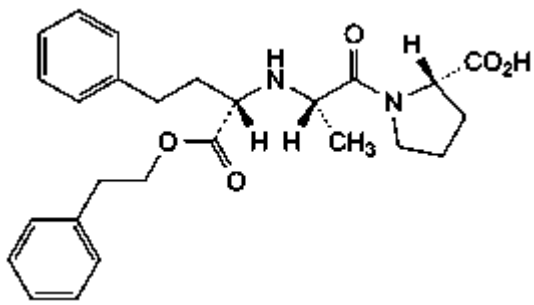
B. (2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoic acid,



C. (2*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid,



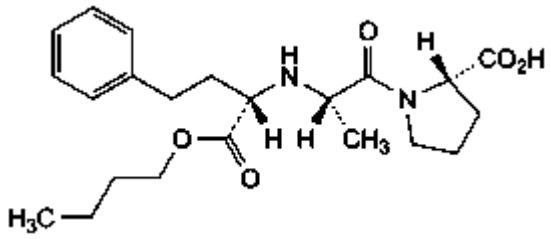
D. ethyl (2*S*)-2-[(3*S*,8a*S*)-3-methyl-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoate,



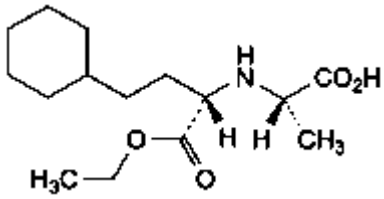
E. (2*S*)-1-[(2*S*)-2-[[(1*S*)-3-phenyl-1-[(2-phenylethoxy)carbonyl]propyl]amino]propanoyl]pyrrolidine-2-carboxylic acid,

www.webofpharma.com

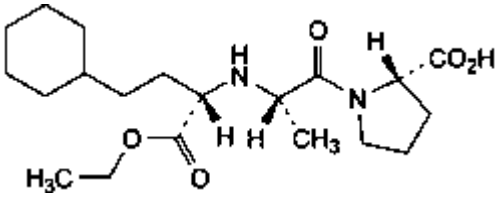
https://thuocngocanh.com/



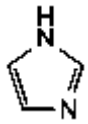
F. (2*S*)-1-[(2*S*)-2-[[(1*S*)-1-(butoxycarbonyl)-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid,



G. (2*S*)-2-[[(1*S*)-3-cyclohexyl-1-(ethoxycarbonyl)propyl]amino]propanoic acid,



H. (2*S*)-1-[(2*S*)-2-[[(1*S*)-3-cyclohexyl-1-(ethoxycarbonyl)propyl]amino]propanoyl]pyrrolidine-2-carboxylic acid,



I. 1*H*-imidazole.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Enalapril Tablets

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Enalapril Tablets contain Enalapril Maleate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of enalapril maleate, $C_{20}H_{28}N_2O_5,C_4H_4O_4$

93.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 20 mg of Enalapril Maleate with 10 mL of *ethanol (90%)* for 10 minutes, centrifuge and use the clear supernatant liquid (if necessary, filter through a 0.45-µm membrane filter).

(2) 0.2% w/v of *enalapril maleate BPCRS* in *ethanol (90%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel plate* (Merck silica gel 60 HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a solution prepared by mixing equal volumes of a 40% w/v solution of *potassium iodide* in *water* and a solution prepared by dissolving 0.85 g of *bismuth oxynitrate* in a mixture of 10 mL of *glacial acetic acid* and 40 mL of *water* and diluting 10 volumes of the mixture with 20 volumes of *glacial acetic acid* and 70 volumes of *water* immediately before use, then spray with *dilute hydrogen peroxide solution*.

MOBILE PHASE

15 volumes of *glacial acetic acid*, 25 volumes of *water* and 60 volumes of *butan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

Dissolve 2.76 g of *sodium phosphate monobasic monohydrate* in 1800 mL of *water* and adjust the pH to 2.2 with *orthophosphoric acid*. Dilute to 2000 mL with *water* and mix well (solution A).

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with *water* if necessary, expected to contain 0.00028% w/v of Enalapril Maleate.
(2) 0.00028% w/v of *enalapril maleate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Alltech Platinum EPS C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 215 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

25 volumes of *acetonitrile R1* and 75 volumes of solution A.

DETERMINATION OF CONTENT

Calculate the total content of enalapril maleate, $C_{20}H_{28}N_2O_5,C_4H_4O_4$, in the medium from the chromatograms obtained and using the declared content of $C_{20}H_{28}N_2O_5,C_4H_4O_4$ in *enalapril maleate BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 2.76 g of *sodium phosphate monobasic monohydrate* in 1800 mL of *water* and adjust the pH to 2.2 with *orthophosphoric acid*. Dilute to 2000 mL with *water* and mix well (solution A).

(1) Shake a quantity of the powdered tablets containing 20 mg of Enalapril Maleate with 100 mL of solution A, mix with the aid of ultrasound and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.002% w/v each of *enalapril maleate BPCRS*, *enalapril diketopiperazine BPCRS* (impurity D), *enalaprilat BPCRS* (impurity C) and *3-phenylpropanoic acid* (impurity 1) in solution A.

(4) 0.002% w/v of *L-alanyl-L-proline* in solution A.

(5) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to enalapril (retention time about 5 minutes) are: maleic acid, about 0.2; L-alanyl-L-proline, about 0.3; impurity C, about 0.4; impurity 1, about 0.5 and impurity D, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the principal peak and the peaks due to impurity C or impurity D, is at least 2.0.

LIMITS

Identify any peaks due to impurities C, D, 1 and maleic acid in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity C by a correction factor of 0.7 and any peak corresponding to impurity 1 by a correction factor of 0.6.

Identify any peak due to L-alanyl-L-proline in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (4).

In the chromatogram obtained with solution (1):

the area of the peak corresponding to impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of the peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity 1 is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any other *secondary peaks*, excluding impurities C, D and 1, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

Disregard any peaks due to maleic acid and L-alanyl-L-proline and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Dissolve 2.76 g of *sodium phosphate monobasic monohydrate* in 1800 mL of *water* and adjust the pH to 2.2 with *orthophosphoric acid*. Dilute to 2000 mL with *water* and mix well (solution A).

(1) Shake a quantity of the powdered tablets containing 20 mg of Enalapril Maleate with 100 mL of solution A, mix with the aid of ultrasound and filter.
(2) 0.02% w/v of *enalapril maleate BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the symmetry factor is no more than 2.0.

DETERMINATION OF CONTENT

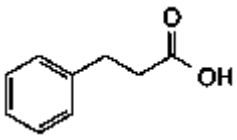
Calculate the content of $C_{20}H_{28}N_2O_5,C_4H_4O_4$ in the tablets using the declared content of $C_{20}H_{28}N_2O_5,C_4H_4O_4$ in *enalapril maleate BPCRS*.

STORAGE

Enalapril Tablets should be protected from light and moisture.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Enalapril Maleate and the following:



1. 3-phenylpropanoic acid (dihydrocinnamic acid)

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

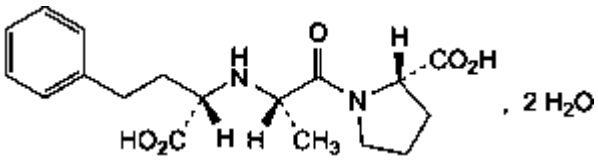
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Enalaprilat Dihydrate

General Notices

(Ph. Eur. monograph 1749)



$C_{18}H_{24}N_2O_5,2H_2O$ 384.4 *84680-54-6*

Action and use

Angiotensin converting enzyme inhibitor.

Ph Eur

DEFINITION

(2*S*)-1-[(2*S*)-2-[[(1*S*)-1-Carboxy-3-phenylpropyl]amino]propanoyl)pyrrolidine-2-carboxylic acid dihydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Very slightly soluble or slightly soluble in water, sparingly soluble in methanol, practically insoluble in acetonitrile.

It shows pseudopolymorphism (*5.9*).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Mulls in *liquid paraffin R*.

www.webofpharma.com

https://thuocngocanh.com/

Comparison *enalaprilat dihydrate CRS*.

If the spectra obtained show differences, expose the substance to be examined and the reference substance to a 98 per cent relative humidity for 3 days using a chamber conditioned with a saturated solution of *calcium sulfate R*. Record new spectra.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.10 g in *water R* and dilute to 100.0 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-53.0 to -56.0 (anhydrous substance).

Dissolve 0.200 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Use freshly prepared solutions.*

Buffer solution Dissolve 1.36 g of *potassium dihydrogen phosphate R* in 950 mL of *water R*. Adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture Buffer solution, *acetonitrile R1*, *methanol R1* (1:2:2 *V/V/V*).

Dissolution mixture Solvent mixture, buffer solution (8:92 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in 2.5 mL of *methanol R1* and dilute to 25.0 mL with the dissolution mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the dissolution mixture. Dilute 5.0 mL of this solution to 10.0 mL with the dissolution mixture.

Reference solution (b) Dissolve 5 mg of *enalaprilat for system suitability CRS* (containing impurity C) in 0.5 mL of *methanol R1* and dilute to 5 mL with the dissolution mixture.

Reference solution (c) Dissolve the contents of a vial of *enalaprilat impurity G CRS* in 1 mL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 70 °C.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: solvent mixture, buffer solution (10:90 *V/V*);

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 50	100 → 90	0 → 10
50 - 80	90	10

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *enalaprilat for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity G.

Relative retention With reference to enalaprilat (retention time = about 21 min): impurity C = about 1.2; impurity G = about 2.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to enalaprilat.

Limits:

— *impurities C, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

7.0 per cent to 11.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

Bacterial endotoxins (*2.6.14*)

Less than 0.1 IU/mg.

ASSAY

Dissolve 0.300 g in *glacial acetic acid R* and dilute to 50 mL with the same solvent. Titrate with *0.1 M perchloric acid*, determining the end point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 34.84 mg of $C_{18}H_{24}N_2O_5$.

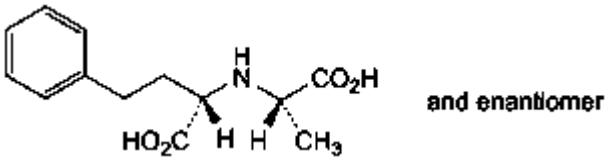
STORAGE

In an airtight container.

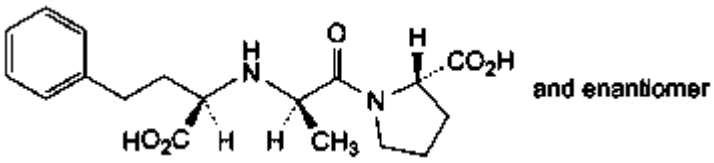
IMPURITIES

Specified impurities C, G.

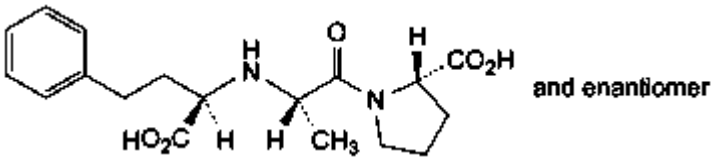
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, D, E, F.



A. (2*SR*)-2-[[(1*SR*)-1-carboxyethyl]amino]-4-phenylbutanoic acid,



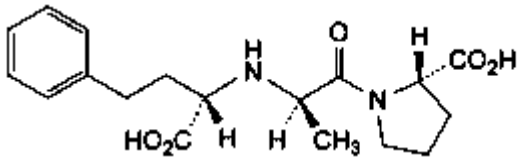
B. (2*SR*)-1-[(2*RS*)-2-[[(1*RS*)-1-carboxy-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid,



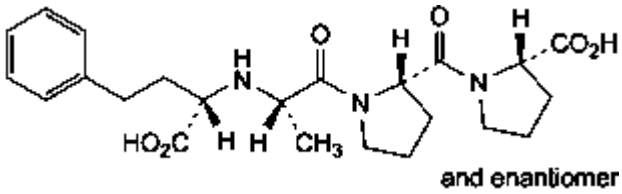
C. (2*SR*)-1-[(2*SR*)-2-[[(1*RS*)-1-carboxy-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid,

www.webofpharma.com

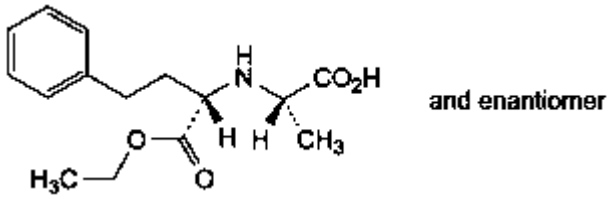
https://thuocngocanh.com/



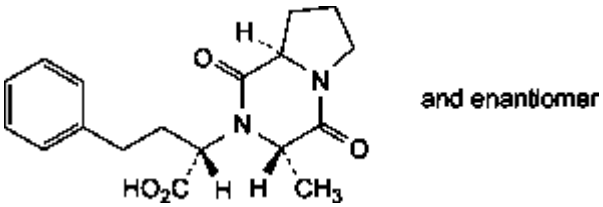
D. (2*SR*)-1-[(2*RS*)-2-[[(1*SR*)-1-carboxy-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid,



E. (2*SR*)-1-[[(2*SR*)-1-[(2*SR*)-2-[[(1*SR*)-1-carboxy-3-phenylpropyl]amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidine-2-carboxylic acid,



F. (2*SR*)-2-[[(1*SR*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoic acid,



G. (2*SR*)-2-[(3*SR*,8a*RS*)-3-methyl-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

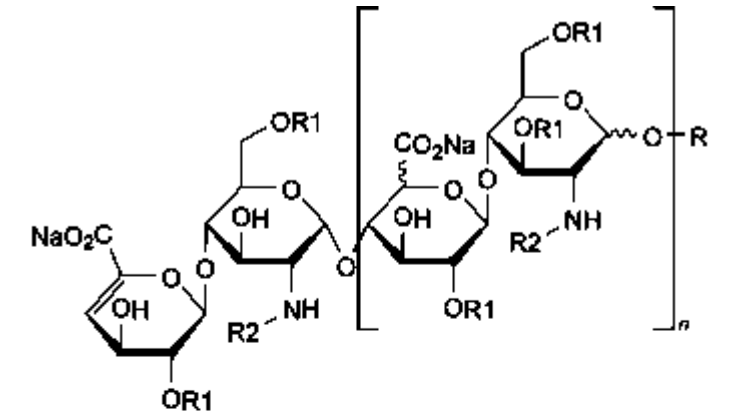
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

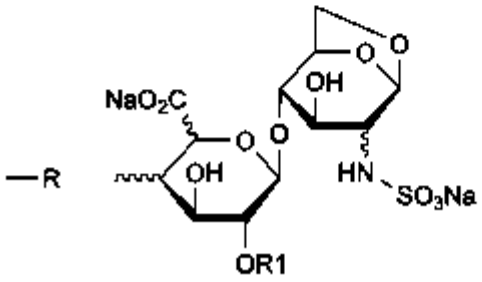
Enoxaparin Sodium

General Notices

(Ph. Eur. monograph 1097)



Structure at the 'reducing end'		
	1,6-anhydro	non 1,6-anhydro
n	0 to 20	1 to 21



R1 = H or SO_3Na R2 = SO_3Na or $CO\text{-}CH_3$

Action and use

Low molecular weight heparin.

Preparation

Enoxaparin Sodium Injection

Ph Eur

DEFINITION

Enoxaparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin consists of a complex set of oligosaccharides that have not yet been

www.webofpharma.com

https://thuocngocanh.com/

completely characterised. Based on current knowledge, the majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain. 15 per cent to 25 per cent of the components have a 1,6-anhydro structure at the reducing end of their chain.

Enoxaparin sodium complies with the monograph Low-molecular-mass heparins (0828) with the modifications and additional requirements below.

The mass-average relative molecular mass ranges between 3800 and 5000, with a characteristic value of about 4500.

The degree of sulfatation is about 2 per disaccharide unit.

The potency is not less than 90 IU and not more than 125 IU of anti-factor Xa activity per milligram, calculated with reference to the dried substance. The anti-factor IIa activity is not less than 20.0 IU and not more than 35.0 IU per milligram, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

PRODUCTION

Enoxaparin is produced by alkaline depolymerisation of benzyl ester derivatives of heparin from porcine intestinal mucosa under conditions that yield a product complying with the structural requirements stated under Definition.

IDENTIFICATION

A. Carry out identification test A as described in the monograph Low-molecular-mass heparins (0828) using enoxaparin sodium CRS.

B. Liquid chromatography (2.2.29): use the normalisation procedure.

Solution A Dissolve 12 mg of sodium tetrahydroborate R in 400 µL of water R and mix using a vortex mixer.

Heparinase solution (a) Dissolve heparinase I R in potassium phosphate buffer solution pH 7.0 R to obtain an activity of 0.4 IU/mL. Store the solution at – 20 °C until use.

Heparinase solution (b) Dissolve heparinase II R in potassium phosphate buffer solution pH 7.0 to obtain an activity of 0.4 IU/mL. Store the solution at – 20 °C until use.

Heparinase solution (c) Dissolve heparinase III R in potassium phosphate buffer solution pH 7.0 R to obtain an activity of 0.4 IU/mL. Store the solution at – 20 °C until use.

Heparinase solution (d) Mix equal volumes of heparinase solution (a), heparinase solution (b) and heparinase solution (c).

Blank solution Gently mix by inversion 20 µL of water R, 70 µL of sodium/calcium acetate buffer solution pH 7.0 R and 100 µL of heparinase solution (d). Place in a water-bath at 25 °C for 48 h. Mix 60 µL of this solution and 10 µL of freshly prepared solution A. Mix and allow to stand at room temperature for 4 h.

Test solution (a) Dissolve 20 mg of the substance to be examined in 1 mL of water R.

Test solution (b) To 20 µL of test solution (a), add 70 µL of sodium/calcium acetate buffer solution pH 7.0 R and 100 µL of heparinase solution (d). Gently mix by inversion and place in a water-bath at 25 °C for 48 h.

Test solution (c) To 60 µL of test solution (b), add 10 µL of freshly prepared solution A. Mix and allow to stand at room temperature for 4 h.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 20 mg of *enoxaparin sodium CRS* in 1 mL of *water R*.

Reference solution (b) To 20 µL of reference solution (a), add 70 µL of *sodium/calcium acetate buffer solution pH 7.0 R* and 100 µL of heparinase solution (d). Gently mix by inversion and place in a water-bath at 25 °C for 48 h.

Reference solution (c) To 60 µL of reference solution (b), add 10 µL of freshly prepared solution A. Mix and allow to stand at room temperature for 4 h.

NOTE: heparinase solutions (a), (b) and (c) can be stored for 3 months at – 20 °C. Test solutions (a) and (b) and reference solutions (a) and (b) must be prepared at the same time; depolymerised test solutions are stable for 1 month at – 20 °C. Test solution (c) and reference solution (c) must also be prepared at the same time.

Precolumn:

— *size*: *l* = 0.01 m, Ø = 4.6 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.280 g of *sodium dihydrogen phosphate R* in 950 mL of *water R*, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: dissolve 140 g of *sodium perchlorate R* in 950 mL of mobile phase A, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with mobile phase A;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	97 → 65	3 → 35
20 - 50	65 → 0	35 → 100
50 - 60	0	100

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 234 nm.

Injection 18 µL of the blank solution, test solution (c) and reference solutions (b) and (c).

www.webofpharma.com

https://thuocngocanh.com/

Identification of disaccharides Use the chromatogram supplied with *enoxaparin sodium CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to the disaccharides listed in Table 1097.-1; use the chromatogram obtained with reference solution (b) to confirm the identity of the peaks due to the 1,6-anhydro derivatives.

Table 1097.-1. – *Correlation between the relative retention of peaks observed in chromatograms obtained with solutions of depolymerised and reduced enoxaparin, with reference to reduced ΔIS (retention time = about 30 min), and molecular masses of the enoxaparin derivatives*

Derivatives	Relative retention	Molecular mass (Da)
Unidentified	< 0.20	741
Reduced ΔIVA	0.20	401
Unidentified	0.20 - 0.46	741
Reduced ΔIVS	0.46	461
Unidentified	0.46 - 0.48	483
Reduced ΔIIA	0.48	503
Unidentified	0.48 - 0.52	503
1,6-anhydro ΔIIS	0.52	443
Unidentified	0.52 - 0.57	503
Reduced ΔIIIA	0.57	503
Unidentified	0.57 - 0.66	533
Reduced ΔIIS	0.66	563
Unidentified	0.66 - 0.76	563
Reduced ΔIIIS	0.76	563
Unidentified	0.76 - 0.85	583
Reduced ΔIA	0.85	605
1,6-anhydro ΔIS	0.88	545
Unidentified	0.88 - 0.97	635
Reduced ΔIIA-IVSglu	0.97	1066
Reduced ΔIS	1.00	665
ΔIS	1.04	665
Unidentified	1.04 - 1.10	1228

www.webofpharma.com

https://thuocngocanh.com/

Derivatives	Relative retention	Molecular mass (Da)
Reduced ΔIIA-IISglu	1.10	1168
Unidentified	1.10 - 1.28	1228
1,6-anhydro ΔIS-IS	1.28	1210
Unidentified	> 1.28	1228

NOTE: depending on the resolution of the column, 1,6-anhydro ΔIIS may be eluted in the form of 2 peaks (mannosamine and glucosamine forms), which are both taken into account as 1,6-anhydro ΔIIS.

Relative retention With reference to reduced ΔIS (retention time = about 30 min): see Table 1097.-1.

System suitability:

— *peak area ratio*: maximum 1.15 for the peaks due to 1,6-anhydro ΔIS-IS and 1,6-anhydro ΔIS in the chromatogram obtained with reference solution (b); maximum 0.02 for the peaks due to ΔIS and reduced ΔIS in the chromatogram obtained with reference solution (c);

— *resolution*: minimum 1.5 between the peaks due to reduced ΔIA and 1,6-anhydro ΔIS in the chromatogram obtained with reference solution (c);

— the content of 1,6-anhydro derivatives in *enoxaparin sodium CRS* is within 1.5 per cent of the assigned content.

Calculation:

Calculate the molar percentage of the 3 main 1,6-anhydro derivatives using the relative molecular masses given in Table 1097.-1 and the following expression:

$$100 \times \frac{Mw}{\sum Mw_x \cdot A_x} \times \left(A_1 + A_2 + A_3\right)$$

Mw	=	mass-average relative molecular mass of enoxaparin (as determined by identification test C);
Mw_x	=	relative molecular mass attributed to derivative *x* according to Table 1097.-1;
A_x	=	area of the peak due to derivative *x*;
A_1	=	area of the peak due to 1,6-anhydro ΔIS;
A_2	=	area of the peak due to 1,6-anhydro ΔIIS;
A_3	=	area of the peak due to 1,6-anhydro ΔIS-IS.

Disregard any peak observed with the blank solution.

Correct the value to the nearest unit.

www.webofpharma.com

https://thuocngocanh.com/

Limit 15 per cent to 25 per cent of components bearing the 1,6-anhydro structure at the reducing end of their chain.

C. Carry out identification test C as described in the monograph *Low-molecular-mass heparins (0828)*. The following requirements apply. The mass-average relative molecular mass ranges between 3800 and 5000. The mass percentage of chains lower than 2000 ranges between 12.0 per cent and 20.0 per cent. The mass percentage of chains between 2000 and 8000 ranges between 68.0 per cent and 82.0 per cent.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dissolve 1.0 g in 10 mL of *water R*.

pH (*2.2.3*)

6.2 to 7.7.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Specific absorbance (*2.2.25*)

14.0 to 20.0 (dried substance), determined at 231 nm.

Dissolve 50.0 mg in 100 mL of *0.01 M hydrochloric acid*.

Benzyl alcohol

Liquid chromatography (*2.2.29*).

Internal standard solution 1 g/L solution of *3,4-dimethylphenol R* in *methanol R*.

Test solution Dissolve about 0.500 g of the substance to be examined in 5.0 mL of *1 M sodium hydroxide*. Allow to stand for 1 h. Add 1.0 mL of *glacial acetic acid R* and 1.0 mL of the internal standard solution and dilute to 10.0 mL with *water R*.

Reference solution Prepare a 0.25 g/L solution of *benzyl alcohol R* in *water R*. Mix 0.50 mL of this solution with 1.0 mL of the internal standard solution and dilute to 10.0 mL with *water R*.

Precolumn:

— *size*: *l* = 0.02 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, *acetonitrile R*, *water R* (5:15:80 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 256 nm.

Injection 20 µL.

From the chromatogram obtained with the reference solution, calculate the ratio (R_1) of the height of the peak due to benzyl alcohol to the height of the peak due to the internal standard. From the chromatogram obtained with the test solution, calculate the ratio (R_2) of the height of the peak due to benzyl alcohol to the height of the peak due to the internal standard.

Calculate the percentage content *m/m* of benzyl alcohol using the following expression:

$$\frac{0.0125 \times R_2}{m \times R_1}$$

m = mass of the substance to be examined, in grams.

Limit:

— *benzyl alcohol*: maximum 0.1 per cent *m/m*.

Sodium (*2.2.23, Method I*)

11.3 per cent to 13.5 per cent (dried substance).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Enoxaparin Sodium Injection

General Notices

Action and use

Low molecular weight heparin.

DEFINITION

Enoxaparin Sodium Injection is a sterile solution of Enoxaparin Sodium in Water for Injections. It may contain, in multidose containers, a suitable antimicrobial preservative.

PRODUCTION

The final product is produced by methods of manufacturing designed to ensure that substances lowering blood pressure are not introduced and to ensure freedom from contamination by over-sulfated glycosaminoglycans. The production method is validated to demonstrate that the product if tested, would comply with the test for Related substances given below.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Activity

The estimated activity for anti-factor Xa is not less than 90% and not more than 110% of the stated activity.

The ratio of anti-factor Xa to anti-factor IIa is not less than 3.3 and not more than 5.3.

IDENTIFICATION

A. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions in the mobile phase.

(1) Dilute the injection to contain 1000 IU of anti-factor Xa per mL.

(2) 1% w/v of *heparin low-molecular-mass for calibration EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a column (30 cm × 7.8 mm) packed with appropriate porous silica beads (5 µm) with a fractionation range for proteins of approximately 15 000 to 100 000 Da (Tosoh Bioscience TSK-GEL G2000SWXL or TSK-GEL G3000SWXL are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use an ambient column temperature.

(e) For detection use a differential refractometer (RI).

(f) Inject 25 µL of each solution.

To calibrate, inject 25 µL of the reference solution and record the chromatogram for a period of time, ensuring complete elution of sample, salt and solvent peaks. Calculate the total area under the RI curve (ΣRI) by numerical integration over the range of interest (i.e. excluding

www.webofpharma.com

https://thuvienthuocngocanh.com/

salt and solvent peaks at the end of the chromatogram as well as the artefact peak (*), that if present, elutes at the same retention time as the peak that would be obtained after injection of sodium sulfate) as shown in Figure 1.

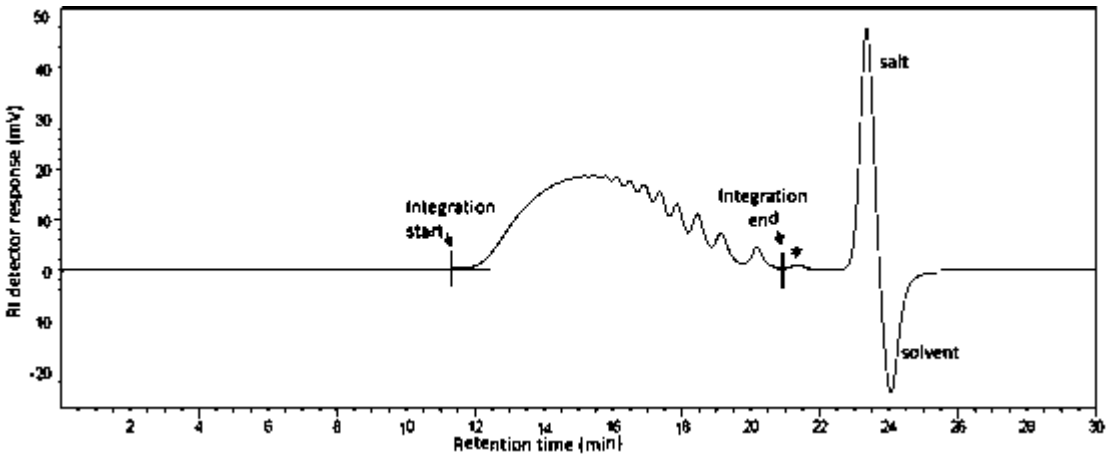


Figure 1 - Example chromatogram of a low-molecular-mass heparin sample analysed using the method described in identification test A indicating peak integration

Calculate the area under the curve up to each point as a percentage of the total area.

Using the leaflet supplied with *heparin low-molecular-mass for calibration EPCRS*, identify those points in the chromatogram for which the percentage of the total area under the curve is closest to the percentage mass fractions listed in the Broad Standard Table, and assign the molecular mass in the table to the corresponding retention time in the chromatogram. A calibration curve for the chromatographic system is derived by fitting a suitable mathematical relationship to the set of retention times and logarithms of the molecular masses. A polynomial of the 3rd degree is recommended.

Inject 25 µL of the test solution and record the chromatogram for a sufficient period of time to ensure complete elution of sample, salt and solvent peaks.

The mass-average relative molecular mass is defined by the following expression:

$$\frac{\sum \left(\mathrm{RI}_i M_i \right)}{\sum \mathrm{RI}_i}$$

where:

RI_i	=	Refractive Index of substance eluting in the fraction *i* (proportional to the mass of the substance);
M_i	=	relative molecular mass corresponding to fraction *i*.

MOBILE PHASE

0.77% w/v of *ammonium acetate*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The mass-average relative molecular mass ranges between 3800 and 5000. The mass percentage of chains lower than 2000 is between 12.0 and 20.0%. The mass percentage of chains between 2000 and 8000 ranges between 68.0 and 82.0%.

B. The ratio of anti-factor Xa activity to anti-factor IIa activity, determined as described under Assay, is not less than 3.3 and not more than 5.3.

C. Yields reaction A characteristic of *sodium salts*, Appendix VI.

TESTS

Clarity and colour of solution

The solution is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* Y_4 *or* BY_4, Appendix IV B, Method II.

Acidity or alkalinity

pH, 5.5 to 7.5, Appendix V L.

Light absorption

The *light absorption*, Appendix II B, of a solution containing the total contents of a single dose container, or 0.4 mL from a multi-dose container, diluted to 100.0 mL with a solution of 0.01M *hydrochloric acid* exhibits a maximum at 231 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions. Solutions (3) to (6) are stable at room temperature for 24 hours.

(1) Dilute the injection with *water for chromatography* to give 5000 IU per mL.

(2) Mix 500 µL of solution (1) and 250 µL of 1M *hydrochloric acid*, add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes. Add 200 µL of 1M *sodium hydroxide* to stop the reaction.

(3) Dissolve 0.25 g of *heparin for physico-chemical analysis EPCRS* in *water for chromatography* and dilute to 2.0 mL with the same solvent. Mix using a vortex mixer until dissolution is complete.

(4) Add 1200 µL of solution (3) to 300 µL of *dermatan sulfate and over-sulfated chondroitin sulfate EPCRS*. Mix using a vortex mixer to homogenise.

(5) Add 400 µL of solution (3) to 100 µL of *water for chromatography* and mix using a vortex mixer. Add 250 µL of 1M *hydrochloric acid*, then add 50 µL of a 25% w/v mL solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of 1M *sodium hydroxide* to stop the reaction.

(6) To 500 µL of solution (4), add 250 µL of 1M *hydrochloric acid*, then add 50 µL of a 25% w/v solution of *sodium nitrite*. Mix gently and allow to stand at room temperature for 40 minutes before adding 200 µL of 1M *sodium hydroxide* to stop the reaction.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 2 mm) packed with *anion-exchange resin* (9 µm) (Dionex Ionpac AS11-HC is suitable) and a stainless steel pre-column (5 cm × 2 mm) packed with *anion-exchange resin* (13 µm) (Dionex Ionpac AG11-HC is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.22 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 202 nm.

(f) Inject 20 µL of solutions (2), (5) and (6).

MOBILE PHASE

Mobile phase A 0.040% w/v of *sodium dihydrogen orthophosphate* in *water for chromatography* adjusted to pH 3.0 with *dilute orthophosphoric acid*.

Mobile phase B 0.040% w/v of *sodium dihydrogen orthophosphate* and 14% w/v of *sodium perchlorate* in *water for chromatography*, adjusted to pH 3.0 with *dilute orthophosphoric acid*, filtered and degassed.

Equilibrate the column with the mobile phase in the initial gradient ratio for at least 15 minutes.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	75	25	isocratic
10-35	75→0	25→100	linear gradient
35-40	0	100	isocratic
40-45	0→75	100→25	linear gradient
45-60	75	25	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to heparin (retention time about 26 minutes) are: dermatan sulfate and chondroitin sulfate, about 0.9; over-sulfated chondroitin sulfate, 1.3.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (5), no peak is present at the retention time of heparin;

in the chromatogram obtained with solution (6), the *resolution* between the peaks due to dermatan sulfate / chondroitin sulfate and over-sulfated chondroitin sulfate is at least 3.0.

LIMITS

In the chromatogram obtained with solution (2):

the area of the peak due to dermatan sulfate and chondroitin sulfate is not greater than half the area of the corresponding peak in the chromatogram obtained with solution (6) (2.0%);

no peaks other than the peak due to dermatan sulfate and chondroitin sulfate are detected.

Sodium

10.2 to 16.9% of Enoxaparin Sodium, when determined by *atomic absorption spectrophotometry*, Appendix II D Method I. For the purposes of this test, assume that 100 IU of anti-factor Xa is equivalent to 1 mg of Enoxaparin Sodium.

www.webofpharma.com

https://thuocngocanh.com/

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 0.01 IU per International Unit of anti-Xa activity.

ASSAY

The anticoagulant activity of low-molecular-mass heparins is determined *in vitro* by two assays which determine its ability to accelerate the inhibition of factor Xa (anti-Xa assay) and thrombin, factor IIa (anti-IIa assay), by antithrombin III.

The International Units for anti-Xa and anti-IIa activity are the activities contained in a stated amount of the International Standard for low-molecular-mass heparin.

Heparin low-molecular-mass for assay EPBRP, calibrated in International Units by comparison with the International Standard using the two assays given below, is used as the reference preparation.

Provided the equivalence with the below methods is demonstrated, the volumes below can be adjusted in order to use automated methods.

For anti-factor Xa activity

Test solutions (1) to *(4)* Prepare a series of 4 independent dilutions of the injection being examined in *tris-chloride buffer pH 7.4;* the concentration range of the solutions should be within 0.025 IU to 0.2 IU of anti-factor Xa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Reference solutions (1) to *(4)* Prepare a series of 4 dilutions of the reference preparation of low-molecular-mass heparin in *tris-chloride buffer pH 7.4;* the concentration range of the solutions should be within 0.025 IU to 0.2 IU of anti-factor Xa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Label 16 tubes in duplicate: T1, T2, T3, T4 for the dilutions of the injection being examined and R1, R2, R3, R4 for the dilutions of the reference preparation. To each tube add 50 µL of *antithrombin III solution R1* and 50 µL of the appropriate dilution of the injection being examined, or the reference preparation. After each addition, mix but do not allow bubbles to form. Treating the tubes in the order R1, R2, R3, R4, T1, T2, T3, T4, T1, T2, T3, T4, R1, R2, R3, R4, allow to equilibrate at 37° (in a water-bath or heating block) for 1 minute and add to each tube 100 µL of *bovine factor Xa solution*. Incubate for exactly 1 minute and add 250 µL of *chromophore substrate R1*. Stop the reaction after exactly 4 minutes by adding 375 µL of *acetic acid*. Transfer the mixtures to semi-micro cuvettes and measure the *absorbance* at 405 nm, Appendix II B, using a suitable reading device. Determine the blank amidolytic activity at the beginning and at the end of the procedure in a similar manner, using *tris-chloride buffer pH 7.4* in place of the reference and test solutions; the 2 blank values do not differ significantly. Calculate the regression of the absorbance on log concentrations of the solutions of the injection being examined and of the reference preparation of low-molecular-mass heparins and calculate the potency of the substance being examined in International Units of anti-factor Xa activity per mL using the usual statistical methods for parallel-line assays.

For anti-factor IIa activity

Test solutions (1) to *(4)* Prepare a series of 4 independent dilutions of the injection being examined in *tris-chloride buffer pH 7.4*; the concentration range should be within 0.015 IU to 0.075 IU of anti-factor IIa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions (1) to *(4)* Prepare a series of 4 independent dilutions of the reference preparation of low-molecular-mass heparin in *tris-chloride buffer pH 7.4*; the concentration range should be within 0.015 IU to 0.075 IU of anti-factor IIa activity per mL and the dilutions chosen should give a linear response when results are plotted as absorbance against log concentration.

Label 16 tubes, in duplicate: T1, T2, T3, T4 for the dilutions of the injection being examined and R1, R2, R3, R4 for the dilutions of the reference preparation. To each tube add 50 µL of *antithrombin III solution R2* and 50 µL of the appropriate dilution of the injection being examined or the reference preparation. After each addition, mix but do not allow bubbles to form. Treating the tubes in the order R1, R2, R3, R4, T1, T2, T3, T4, T1, T2, T3, T4, R1, R2, R3, R4, allow to equilibrate at 37° (in a water-bath or heating block) for 1 minute and add to each tube 100 µL of *human thrombin solution*. Incubate for exactly 1 minute and add 250 µL of *chromophore substrate R2*. Stop the reaction after exactly 4 minutes by adding 375 µL of *acetic acid*. Transfer the mixtures to semi-micro cuvettes and measure the *absorbance* at 405 nm, Appendix II B, using a suitable reading device. Determine the blank amidolytic activity at the beginning and at the end of the procedure in a similar manner, using *tris-chloride buffer pH 7.4* in place of the reference and test solutions; the 2 blank values do not differ significantly. Calculate the regression of the absorbance on log concentrations of the solutions of the substance to be examined and of the reference preparation of low-molecular-mass heparins, and calculate the potency of the substance being examined in International Units of anti-factor IIa activity per mL using the usual statistical methods for parallel-line assays.

LABELLING

The label states the number of IU (Units) of anti-factor Xa per unit volume.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

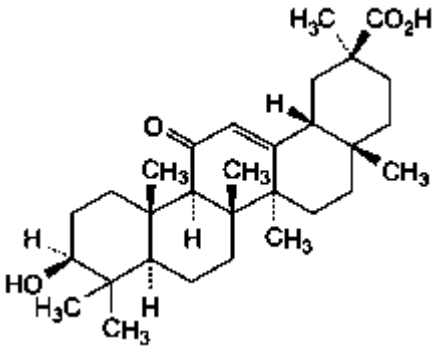
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Enoxolone

General Notices

(Ph. Eur. monograph 1511)



$C_{30}H_{46}O_4$ 470.7 *471-53-4*

Action and use

Treatment of benign peptic ulcer disease.

Ph Eur

DEFINITION

3β-Hydroxy-11-oxoolean-12-en-30-oic acid (glycyrrhetinic acid).

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white crystalline powder.

Solubility

Practically insoluble in water, soluble in anhydrous ethanol, sparingly soluble in methylene chloride.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison enoxolone CRS.

If the spectra obtained in the solid state show differences, dissolve 0.2 g of the substance to be examined and 0.2 g of the reference substance separately in 6 mL of anhydrous ethanol R. Boil under a reflux condenser for 1 h and add 6 mL of water R. A precipitate is formed. Cool to about 10 °C and filter with the aid of vacuum. Wash the precipitate with 10 mL of ethanol (96 per cent) R, dry in an oven at 80 °C and record new spectra.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methylene chloride R and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of enoxolone CRS in methylene chloride R and dilute to 10 mL with the same solvent.

Plate TLC silica gel plate R.

Mobile phase glacial acetic acid R, acetone R, methylene chloride R (5:10:90 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air for 5 min.

Detection Spray with anisaldehyde solution R and heat at 100-105 °C for 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 50 mg in 10 mL of methylene chloride R. To 2 mL of this solution, add 1 mL of acetic anhydride R and 0.3 mL of sulfuric acid R. A pink colour is produced.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, Method II).

Dissolve 0.1 g in anhydrous ethanol R and dilute to 10 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Specific optical rotation (2.2.7)

+ 145 to + 154 (dried substance).

Dissolve 0.50 g in *dioxan R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *enoxolone impurity A CRS* in *tetrahydrofuran R* and dilute to 5 mL with the same solvent. To 2.0 mL of the solution, add 2.0 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *enoxolone for peak identification CRS* (containing impurities B and C) in 2 mL of *tetrahydrofuran R* using sonication, and dilute to 5 mL with a 1.36 g/L solution of *sodium acetate R* adjusted to pH 4.8 with *glacial acetic acid R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 430 volumes of *tetrahydrofuran R* and 570 volumes of a 1.36 g/L solution of *sodium acetate R* adjusted to pH 4.8 with *glacial acetic acid R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 20 µL.

Run time 2 times the retention time of enoxolone.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram supplied with *enoxolone for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B and C.

Relative retention With reference to enoxolone (retention time = about 21.5 min): impurity B = about 0.5; impurity A = about 0.9; impurity C = about 1.3.

System suitability:

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum of 2.0 between the peaks due to impurity A and enoxolone in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— for each impurity, use the concentration of enoxolone in reference solution (a).

Limits:

— *impurity B*: maximum 0.7 per cent;

— *impurities A and C*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.330 g in 40 mL of *dimethylformamide R*. Titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically (2.2.20). Carry out a blank titration.

1 mL of *0.1 M tetrabutylammonium hydroxide* is equivalent to 47.07 mg of $C_{30}H_{46}O_4$.

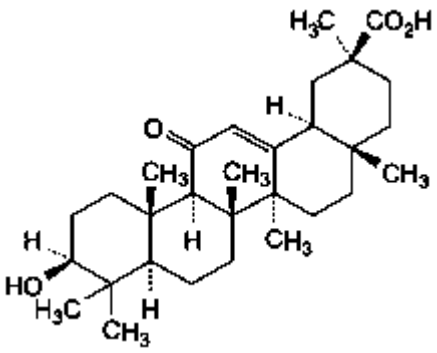
STORAGE

Protected from light.

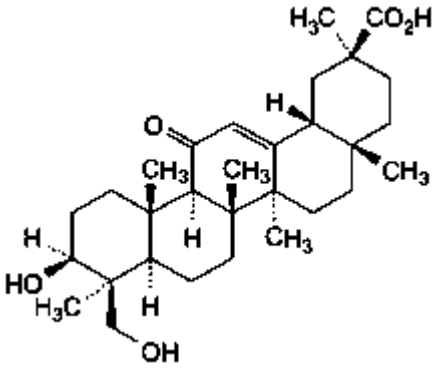
IMPURITIES

www.webofpharma.com

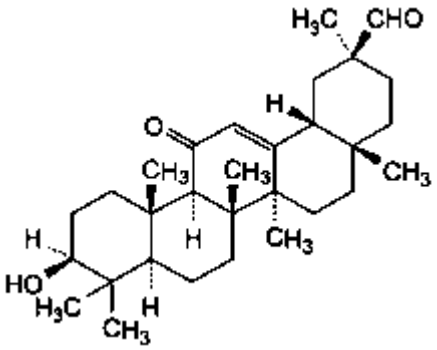
https://thuocngocanh.com/



A. 3β-hydroxy-11-oxo-18α-olean-12-en-30-oic acid (18α-glycyrrhetinic acid),



B. 3β,24-dihydroxy-11-oxoolean-12-en-30-oic acid,



C. 3β-hydroxy-11-oxoolean-12-en-30-al (glycyrrhetaldehyde).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

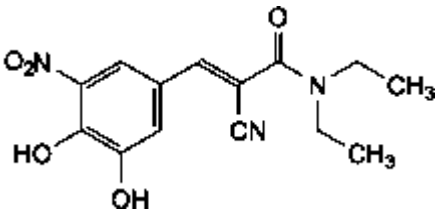
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Entacapone

General Notices

(Ph. Eur. monograph 2574)



$C_{14}H_{15}N_3O_5$ 305.3 *130929-57-6*

Action and use

Catechol-O-methyl transferase inhibitor; treatment of Parkinson's disease.

Ph Eur

DEFINITION

(2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Greenish-yellow or yellow powder.

Solubility

Practically insoluble in water, soluble or sparingly soluble in acetone, slightly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *entacapone CRS*.

www.webofpharma.com

https://thuocngocanh.com/

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Use freshly prepared solutions.*

Solvent mixture *tetrahydrofuran R*, *methanol R* (30:70 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *entacapone impurity A CRS* in the solvent mixture, add 5.0 mL of test solution (a) and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 20.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (b) to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of *entacapone CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped propyl-2-phenylsilyl amorphous organosilica polymer R* (5 µm).

Mobile phase Mix 2 volumes of *tetrahydrofuran R*, 44 volumes of *methanol R* and 54 volumes of a 2.34 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 2.1 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 300 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Run time 2.5 times the retention time of entacapone.

Relative retention With reference to entacapone (retention time = about 17 min): impurity A = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity A and entacapone.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *sum of impurities other than A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{14}H_{15}N_3O_5$ from the declared content of *entacapone CRS*.

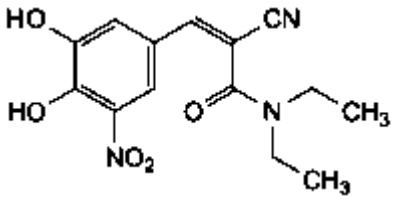
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A.*

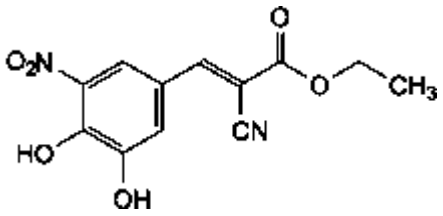
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F, G, H, I.*



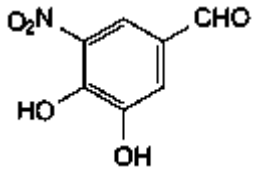
A. (2*Z*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide,

www.webofpharma.com

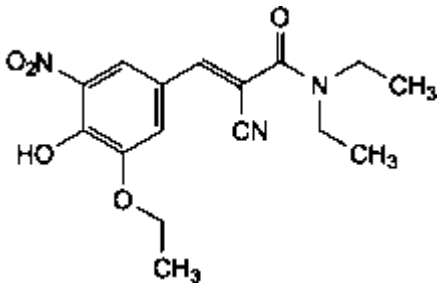
https://thuocngocanh.com/



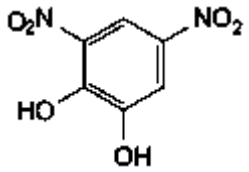
B. ethyl (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)prop-2-enoate,



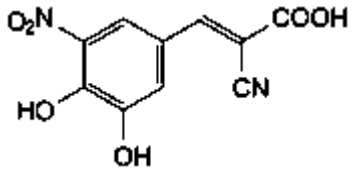
C. 3,4-dihydroxy-5-nitrobenzaldehyde,



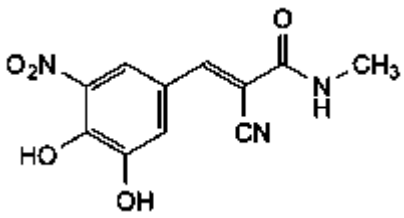
D. (2*E*)-2-cyano-3-(3-ethoxy-4-hydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide,



E. 3,5-dinitrobenzene-1,2-diol,



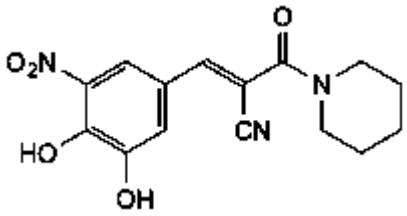
F. (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)prop-2-enoic acid,



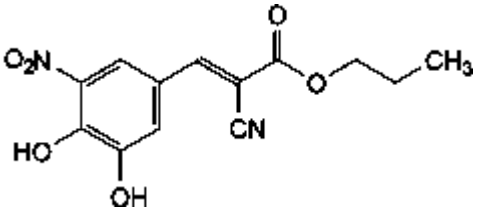
G. (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*-methylprop-2-enamide,

www.webofpharma.com

https://thuocngocanh.com/



H. (2*E*)-3-(3,4-dihydroxy-5-nitrophenyl)-2-(piperidin-1-ylcarbonyl)prop-2-ennitrile,



I. propyl (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)prop-2-enoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

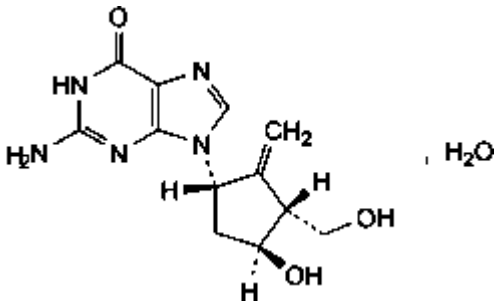
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Entecavir Monohydrate

General Notices

(Ph. Eur. monograph 2815)



$C_{12}H_{15}N_5O_3,H_2O$ 295.3 *209216-23-9*

Ph Eur

DEFINITION

2-Amino-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one monohydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, in anhydrous ethanol and in heptane, slightly soluble in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *entecavir monohydrate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

If the spectra obtained show differences, suspend 50 mg of the substance to be examined and 50 mg of the reference substance separately in 5 mL of hot *water R*. Swirl protected from light and heat until a clear solution is obtained. Allow to cool and filter the precipitates *in vacuo*. Dry the precipitates for 12 h in a desiccator and record new spectra using the residues.

TESTS

Specific optical rotation (2.2.7)

+ 24 to + 30 (anhydrous substance), measured at 25 °C.

Dissolve 0.25 g in 10 mL of a mixture of equal volumes of *dimethylformamide R* and *methanol R* and dilute to 25.0 mL with the same mixture of solvents.

Impurity F

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in 10 mL of *methanol R* using sonication, and dilute to 25.0 mL with the same solvent.

Reference solution Dissolve 2.5 mg of *entecavir impurity F CRS* in 20 mL of *methanol R* using sonication, and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *trifluoroacetic acid R*;

— *mobile phase B*: 0.1 per cent *V/V* solution of *trifluoroacetic acid R* in *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	65 → 53	35 → 47

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Retention time Impurity F = about 6 min.

www.webofpharma.com

https://thuocngocanh.com/

Calculation of percentage content:

— for impurity F, use the concentration of impurity F in the reference solution.

Limit:

— *impurity F*: maximum 0.10 per cent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in 10 mL of *methanol R* using sonication, and dilute to 25.0 mL with the same solvent. Dilute 2.0 mL of the solution to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 25.0 mg of *entecavir monohydrate CRS* in 10 mL of *methanol R* using sonication, and dilute to 25.0 mL with the same solvent. Dilute 2.0 mL of the solution to 10.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of *entecavir for system suitability CRS* (containing impurities A and C) in 1 mL of *methanol R* using sonication, and dilute to 5.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water for chromatography R* (3:97 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	100	0
8 - 50	100 → 77	0 → 23
50 - 75	77 → 17	23 → 83

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *entecavir for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and C.

Relative retention With reference to entecavir (retention time = about 21 min): impurity A = about 0.9; impurity C = about 1.03.

System suitability Reference solution (c):

— *resolution*: minimum 3.5 between the peaks due to impurity A and entecavir; minimum 2.0 between the peaks due to entecavir and impurity C.

Calculation of percentage contents:

— for each impurity, use the concentration of entecavir monohydrate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak with a relative retention with reference to entecavir of about 3.4 (impurity F).

Water (*2.5.32*)

5.5 per cent to 7.0 per cent, determined on 30.0 mg by direct sample introduction.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{12}H_{15}N_5O_3$ taking into account the assigned content of *entecavir monohydrate CRS*.

STORAGE

Protected from light.

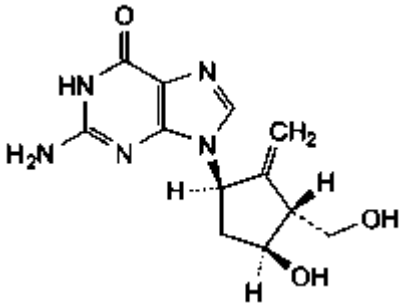
IMPURITIES

Specified impurities *F.*

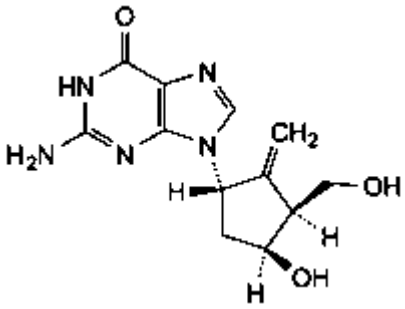
www.webofpharma.com

https://thuocngocanh.com/

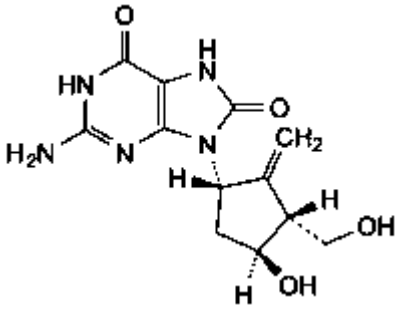
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E.*



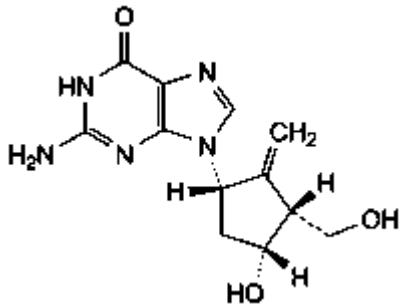
A. 2-amino-9-[(1*R*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one,



B. 2-amino-9-[(1*S*,3*S*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one,



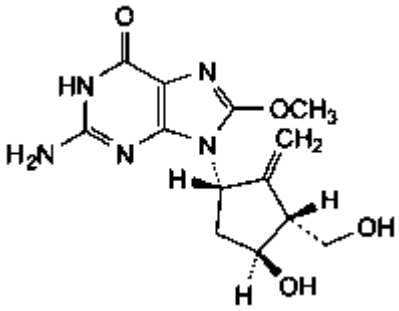
C. 2-amino-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-7,9-dihydro-1*H*-purine-6,8-dione,



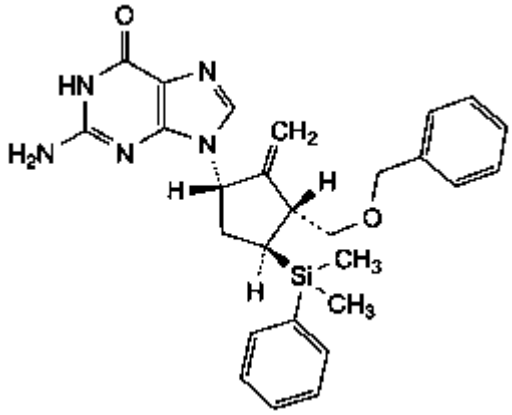
D. 2-amino-9-[(1*S*,3*R*,4*R*)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one,

www.webofpharma.com

https://thuocngocanh.com/



E. 2-amino-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-8-methoxy-1,9-dihydro-6*H*-purin-6-one,



F. 2-amino-9-[(1*S*,3*R*,4*S*)-3-[(benzyloxy)methyl]-4-[dimethyl(phenyl)silyl]-2-methylidenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

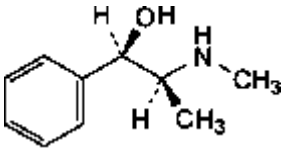
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Ephedrine

General Notices

Anhydrous Ephedrine

(Ph. Eur. monograph 0488)



$C_{10}H_{15}NO$ 165.2 *299-42-3*

Action and use

Adrenoceptor agonist.

Ph Eur

DEFINITION

Ephedrine contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, soluble in water, very soluble in ethanol (96 per cent).

It melts at about 36 °C.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D, E.

A. Specific optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with the base isolated from *ephedrine hydrochloride CRS*. Examine the substances in discs prepared as follows: dissolve 40 mg of the substance to be examined in

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *water R*, add 1 mL of *dilute sodium hydroxide solution R* and 4 mL of *chloroform R* and shake; dry the organic layer over 0.2 g of *anhydrous sodium sulfate R*; prepare a blank disc using about 0.3 g of *potassium bromide R*; apply dropwise to the disc 0.1 mL of the organic layer, allowing the solvent to evaporate between applications; dry the disc at 50 °C for 2 min. Repeat the operations using 50 mg of *ephedrine hydrochloride CRS*.

C. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 10 mg in 1 mL of *water R*. Add 0.2 mL of *strong sodium hydroxide solution R* and 0.2 mL of *copper sulfate solution R*. A violet colour is produced. Add 2 mL of *ether R* and shake. The ether layer is purple and the aqueous layer blue.

E. Water (see Tests).

TESTS

Appearance of solution

Dissolve 0.25 g in *water R* and dilute to 10 mL with the same solvent. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

Dissolve 2.25 g in 15 mL of *dilute hydrochloric acid R* and dilute to 50.0 mL with *water R*. The specific optical rotation is -41 to -43, calculated with reference to the anhydrous substance.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a) Dissolve 0.2 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 25 mg of *ephedrine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 200 mL with *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 5 volumes of *chloroform R*, 15 volumes of *concentrated ammonia R* and 80 volumes of *2-propanol R*. Allow the plate to dry in air and spray with *ninhydrin solution R*. Heat at 110 °C for 5 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). Disregard any spot of lighter colour than the background.

Chlorides

Dissolve 0.17 g in 10 mL of *water R*. Add 5 mL of *dilute nitric acid R* and 0.5 mL of *silver nitrate solution R1*. Allow to stand for 2 min, protected from bright light. Any opalescence in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 mL of *chloride standard solution (5 ppm Cl) R*, 5 mL of *dilute nitric acid R* and 0.5 mL of *silver nitrate solution R1* (290 ppm).

www.webofpharma.com

https://thuocngocanh.com/

Water (*2.5.12*)

Not more than 0.5 per cent, determined on 2.000 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 5 mL of *alcohol R* and add 20.0 mL of *0.1 M hydrochloric acid*. Using 0.05 mL of *methyl red solution R* as indicator, titrate with *0.1 M sodium hydroxide* until a yellow colour is obtained.

1 mL of *0.1 M hydrochloric acid* is equivalent to 16.52 mg of $C_{10}H_{15}NO$.

STORAGE

Store protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ephedrine Elixir

General Notices

Ephedrine Oral Solution

Action and use

Adrenoceptor agonist.

DEFINITION

Ephedrine Elixir is an *oral solution* containing 0.3% w/v of Ephedrine Hydrochloride in a suitable flavoured vehicle containing a sufficient volume of Ethanol (96%) or of an appropriate Dilute Ethanol to give a final concentration of 12% v/v of ethanol.

The elixir complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ephedrine hydrochloride, $C_{10}H_{15}NO,HCl$

0.27 to 0.33% w/v.

IDENTIFICATION

A. To 30 mL of the elixir add 2 mL of *2M hydrochloric acid*, extract with two 20-mL quantities of *ether* and discard the ether. Add sufficient 5 M *ammonia* to the aqueous phase to make it alkaline, extract with two 30-mL quantities of *ether*, wash the combined ether extracts with three 15-mL quantities of *water*, dry with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ephedrine *(RS 121)*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (4).

TESTS

Ethanol content

11 to 13% v/v, Appendix VIII F.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add sufficient 5M *ammonia* to 50 mL of the elixir to make it alkaline, extract with two 100-mL quantities of *ether*, wash the combined extracts with 10 mL of *water*, dry with *anhydrous sodium sulfate*, filter and evaporate the filtrate to dryness. Dissolve the oily residue in sufficient *methanol* to produce 5 mL.

(2) Dilute 1 volume of solution (1) to 10 volumes with *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

(3) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

(4) 0.30% w/v of *ephedrine hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution* and heat at 100° for 5 minutes.

MOBILE PHASE

5 volumes of *chloroform*, 15 volumes of 13.5M *ammonia* and 80 volumes of *propan-2-ol*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3). Disregard any spot of lighter colour than the background.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the elixir containing 60 mg of Ephedrine Hydrochloride to 50 mL with *methanol (65%)*.

(2) 0.12% w/v of *ephedrine hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.005M *dioctyl sodium sulfosuccinate* in a mixture of 1 volume of *glacial acetic acid*, 35 volumes of *water* and 65 volumes of *methanol*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the elixir, Appendix V G, and calculate the content of $C_{10}H_{15}NO,HCl$, weight in volume, using the declared content of $C_{10}H_{15}NO,HCl$ in *ephedrine hydrochloride BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

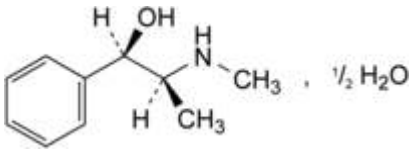
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Ephedrine Hemihydrate

General Notices

(Ph. Eur. monograph 0489)

NOTE: *The name Ephedrine was formerly used in the United Kingdom.*



$C_{10}H_{15}NO,½H_2O$ 174.2 *50906-05-3*

Action and use

Adrenoceptor agonist.

Ph Eur

DEFINITION

Ephedrine hemihydrate contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (1*R*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, soluble in water, very soluble in ethanol (96 per cent).

It melts at about 42 °C, determined without previous drying.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D, E.

A. Specific optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with the base isolated from *ephedrine hydrochloride CRS*. Examine the substances in discs prepared as follows: dissolve 40 mg of the substance to be examined in

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *water R*, add 1 mL of *dilute sodium hydroxide solution R* and 4 mL of *chloroform R* and shake; dry the organic layer over 0.2 g of *anhydrous sodium sulfate R*; prepare a blank disc using about 0.3 g of *potassium bromide R*; apply dropwise to the disc 0.1 mL of the organic layer, allowing the solvent to evaporate between applications; dry the disc at 50 °C for 2 min. Repeat the operations using 50 mg of *ephedrine hydrochloride CRS*.

C. Examine the chromatograms obtained in the test for related substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Dissolve about 10 mg in 1 mL of *water R*. Add 0.2 mL of *strong sodium hydroxide solution R* and 0.2 mL of *copper sulfate solution R*. A violet colour is produced. Add 2 mL of *ether R* and shake. The ether layer is purple and the aqueous layer blue.

E. Water (see Tests).

TESTS

Appearance of solution

Dissolve 0.25 g in *water R* and dilute to 10 mL with the same solvent. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

Dissolve 2.25 g in 15 mL of *dilute hydrochloric acid R* and dilute to 50.0 mL with *water R*. The specific optical rotation is -41 to -43, calculated with reference to the anhydrous substance.

Related substances

Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution (a) Dissolve 0.2 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 25 mg of *ephedrine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 200 mL with *methanol R*.

Apply separately to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 5 volumes of *chloroform R*, 15 volumes of *concentrated ammonia R* and 80 volumes of *2-propanol R*. Allow the plate to dry in air and spray with *ninhydrin solution R*. Heat at 110 °C for 5 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). Disregard any spot of lighter colour than the background.

Chlorides

Dissolve 0.18 g in 10 mL of *water R*. Add 5 mL of *dilute nitric acid R* and 0.5 mL of *silver nitrate solution R1*. Allow to stand for 2 min, protected from bright light. Any opalescence in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 mL of *chloride standard solution (5 ppm Cl) R*, 5 mL of *dilute nitric acid R* and 0.5 mL of *silver nitrate solution R1* (280 ppm).

www.webofpharma.com

https://thuocngocanh.com/

Water (*2.5.12*)

4.5 per cent to 5.5 per cent, determined on 0.300 g by the semi-micro determination of water.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 5 mL of *alcohol R* and add 20.0 mL of *0.1 M hydrochloric acid*. Using 0.05 mL of *methyl red solution R* as indicator, titrate with *0.1 M sodium hydroxide* until a yellow colour is obtained.

1 mL of *0.1 M hydrochloric acid* is equivalent to 16.52 mg of $C_{10}H_{15}NO$.

STORAGE

Store protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

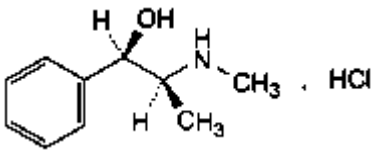
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ephedrine Hydrochloride

General Notices

(Ph. Eur. monograph 0487)



$C_{10}H_{16}ClNO$ 201.7 *50-98-6*

Action and use

Adrenoceptor agonist.

Preparations

Ephedrine Elixir

Ephedrine Nasal Drops

Ephedrine Hydrochloride Tablets

Ephedrine Injection

Ph Eur

DEFINITION

(1*R*,2*S*)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, soluble in ethanol (96 per cent).

mp

About 219 °C.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *ephedrine hydrochloride CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 10 mg of *ephedrine hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *methylene chloride R*, *concentrated ammonia R*, *2-propanol R* (5:15:80 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R*; heat at 110 °C for 5 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. To 0.1 mL of solution S (see Tests) add 1 mL of *water R*, 0.2 mL of *copper sulfate solution R* and 1 mL of *strong sodium hydroxide solution R*. A violet colour is produced. Add 2 mL of *methylene chloride R* and shake. The lower (organic) layer is dark grey and the upper (aqueous) layer is blue.

E. To 5 mL of solution S (see Tests) add 5 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 5.00 g in *distilled water R* and dilute to 50.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.4 mL of *0.01 M hydrochloric acid*. The solution is red.

Specific optical rotation (*2.2.7*)

-33.5 to -35.5 (dried substance).

Dilute 12.5 mL of solution S to 25.0 mL with *water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 75 mg of the substance to be examined in the mobile phase and dilute to 10 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *pseudoephedrine hydrochloride CRS* in the mobile phase and dilute to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical *phenylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Mix 6 volumes of *methanol R* and 94 volumes of a 11.6 g/L solution of *ammonium acetate R* adjusted to pH 4.0 with *glacial acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 257 nm.

Injection 20 µL.

Run time 2.5 times the retention time of ephedrine.

Relative retention With reference to ephedrine (retention time = about 8 min): impurity B = about 1.1; impurity A = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to ephedrine and impurity B.

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.4;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *sum of impurities other than A*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulfates (*2.4.13*)

Maximum 100 ppm, determined on solution S.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 mL of *ethanol (96 per cent) R* and add 5.0 mL of *0.01 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 20.17 mg of $C_{10}H_{16}ClNO$.

STORAGE

Protected from light.

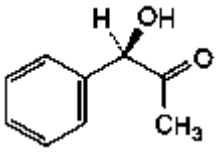
IMPURITIES

Specified impurities *A*.

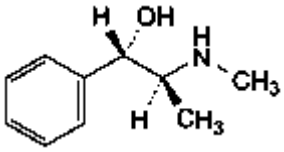
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B*.

www.webofpharma.com

https://thuocngocanh.com/



A. (–)-(1*R*)-1-hydroxy-1-phenylpropan-2-one,



B. (1*S*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol (pseudoephedrine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ephedrine Hydrochloride Tablets

General Notices

Action and use

Adrenoceptor agonist.

DEFINITION

Ephedrine Hydrochloride Tablets contain Ephedrine Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ephedrine hydrochloride, $C_{10}H_{15}NO,HCl$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the tablets containing 0.1 g of Ephedrine Hydrochloride with 20 mL of 0.1M *hydrochloric acid*, filter, wash the filtrate with two 20 mL quantities of *chloroform* and discard the chloroform. Make the aqueous layer alkaline with 5M *ammonia* and extract with two 30 mL quantities of a mixture of 3 volumes of *chloroform* and 1 volume of *ethanol (96%)*. Dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate to a low volume at a pressure of 2 kPa. Prepare a disc using 0.3 g of *potassium bromide*, apply the chloroform solution to the surface of the disc and heat at 50° for 2 minutes. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of ephedrine *(RS 121)*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (3).

C. Triturate a quantity of the powdered tablets containing 0.4 g of Ephedrine Hydrochloride with two 10 mL quantities of *chloroform* and discard the chloroform. Macerate the residue with 30 mL of warm *ethanol (96%)* for 20 minutes, filter, evaporate the filtrate to dryness on a water bath and dry the residue at 80°. Dissolve 10 mg of the residue in 1 mL of *water* and add 0.1 mL of *weak copper sulfate solution* followed by 1 mL of 5M *sodium hydroxide*; a violet colour is produced. Add 1 mL of *ether* and shake; the ether layer is purple and the aqueous layer is blue.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing 0.10 g of Ephedrine Hydrochloride with 5 mL of *methanol*, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 10 volumes with *methanol*.

(3) 0.20% w/v of *ephedrine hydrochloride BPCRS* in *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

(4) Dilute 1 volume of solution (1) to 200 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution* and heat at 110° for 5 minutes.

MOBILE PHASE

5 volumes of *chloroform*, 15 volumes of 13.5M *ammonia* and 80 volumes of *propan-2-ol*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4). Disregard any spot of lighter colour than the background.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Ephedrine Hydrochloride with 30 mL of *methanol* for 10 minutes, add sufficient *water* to produce 50 mL, filter through glass-fibre paper (Whatman GF/C is suitable) and use the filtrate.

(2) 0.1% w/v of *ephedrine hydrochloride BPCRS* in methanol (60%).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable)

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.005M *dioctyl sodium sulfosuccinate* in a mixture of 1 volume of *glacial acetic acid*, 35 volumes of *water* and 65 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{15}NO,HCl$ using the declared content of $C_{10}H_{15}NO,HCl$ in *ephedrine hydrochloride BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ephedrine Injection

General Notices

Action and use

Adrenoceptor agonist; reversal of hypotension from spinal or epidural anaesthesia.

DEFINITION

Ephedrine Injection is a sterile solution of Ephedrine Hydrochloride. It is supplied as a ready-to-use solution in Water for Injections or it is prepared immediately before use in accordance with the manufacturer's instructions from Ephedrine Sterile Concentrate.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

When supplied as a ready-to-use solution, the injection complies with the following requirements.

Content of ephedrine hydrochloride, $C_{10}H_{15}NO,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the injection containing 10 mg of Ephedrine Hydrochloride add 2 mL of *2M hydrochloric acid*, shake with two 20-mL quantities of *dichloromethane* and discard the dichloromethane. Add 5M *ammonia* until the aqueous layer is alkaline, extract with two 30-mL quantities of a mixture of 3 volumes of *dichloromethane* and 1 volume of *ethanol*, dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate to dryness at a pressure of 2 kPa, heating gently to remove the last traces of solvent. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ephedrine hydrochloride *(RS 436)*.

TESTS

Acidity or alkalinity

pH, 4.5 to 7.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the injection, if necessary, with sufficient of the mobile phase to produce a solution containing 0.75% w/v of Ephedrine Hydrochloride.

(2) Dilute 1 volume of solution (1) to 500 volumes with mobile phase.

(3) 0.01% w/v of *ephedrine hydrochloride BPCRS* and 0.01% w/v of *pseudoephedrine hydrochloride BPCRS* in mobile phase.

(4) Dilute 1 volume of solution (2) to 10 volumes with mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenyl silica gel for chromatography* (5 µm) (Spherisorb Phenyl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 257 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of the peak due to ephedrine.

MOBILE PHASE

6 volumes of *methanol* and 94 volumes of a 1.16% w/v solution of *ammonium acetate* adjusted to pH 4.0 using *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of ephedrine is about 13 minutes and the retention time of pseudoephedrine is about 16 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ephedrine and pseudoephedrine is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.02%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the injection with *methanol (80%)* to produce a solution containing 0.1% w/v of Ephedrine Hydrochloride.

(2) 0.1% w/v of *ephedrine hydrochloride BPCRS* in *methanol (65%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 263 nm.

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.005M *dioctyl sodium sulfosuccinate* in a mixture of 1 volume of *glacial acetic acid*, 35 volumes of *water* and 65 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{15}NO,HCl$ in the injection using the declared content of $C_{10}H_{15}NO,HCl$ in *ephedrine hydrochloride BPCRS*.

EPHEDRINE STERILE CONCENTRATE

DEFINITION

Ephedrine Sterile Concentrate is a sterile solution of Ephedrine Hydrochloride in Water for Injections.

The concentrate complies with the requirements for Concentrates for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of ephedrine hydrochloride, $C_{10}H_{15}NO,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the concentrate containing 10 mg of Ephedrine Hydrochloride add 2 mL of *2M hydrochloric acid*, shake with two 20-mL quantities of *dichloromethane* and discard the dichloromethane. Add 5M *ammonia* until the aqueous layer is alkaline, extract with two 30-mL quantities of a mixture of 3 volumes of *dichloromethane* and 1 volume of *ethanol*, dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate to dryness at a pressure of 2 kPa, heating gently to remove the last traces of solvent. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ephedrine hydrochloride *(RS 436)*.

TESTS

Acidity

pH, 4.5 to 7.0, Appendix V L.

Related substances

Carry out the method described in the requirements for the ready to use injection.

ASSAY

Carry out the Assay described in the requirements for the ready to use injection.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ephedrine Nasal Drops

General Notices

Action and use

Adrenoceptor agonist.

DEFINITION

Ephedrine Nasal Drops are a solution of Ephedrine Hydrochloride in a suitable aqueous vehicle.

The nasal drops comply with the requirements stated under Nasal Preparations and with the following requirements.

Content of ephedrine hydrochloride, $C_{10}H_{15}NO,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the nasal drops containing 0.1 g of Ephedrine Hydrochloride add 2 mL of 2M *hydrochloric acid*, shake with two 20 mL quantities of *chloroform* and discard the chloroform. Add 5M *ammonia* until the aqueous layer is alkaline, extract with two 30 mL quantities of a mixture of 3 volumes of *chloroform* and 1 volume of *ethanol*, dry the combined extracts over *anhydrous sodium sulfate*, filter and evaporate to dryness at a pressure of 2 kPa, heating gently to remove the last traces of solvent. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ephedrine *(RS 121)*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (4).

TESTS

Acidity or alkalinity

pH, 4.0 to 7.0, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel precoated plate (Merck silica gel 60 plates are suitable) and a mixture of 80 volumes of *propan-2-ol*, 15 volumes of 13.5M *ammonia* and 5 volumes of *chloroform* as the mobile phase. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) use the nasal drops diluted, if necessary, with *water* to contain 0.5% w/v of Ephedrine Hydrochloride. For solution (2) dilute 1 volume of solution (1) to 5 volumes with *methanol*. For solution (3) dilute 1 volume of solution (1) to 200 volumes with *water*. Solution (4) contains 0.1% w/v of *ephedrine hydrochloride BPCRS* in *methanol*. After removal of the plate, allow it to dry in air, spray with *ninhydrin solution* and heat at 100° for 5 minutes. Any *secondary spot* in the

www.webofpharma.com

https://thuocngocanh.com/

chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3). Disregard any spot of lighter colour than the background and any spot remaining on the line of application.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) is a 0.1% w/v solution of *ephedrine hydrochloride BPCRS* in *methanol (65%)*. For solution (2) dilute the nasal drops with *methanol (80%)* to contain 0.1% w/v of Ephedrine Hydrochloride.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable), (b) 0.005M *dioctyl sodium sulfosuccinate* in a mixture of 65 volumes of *methanol*, 35 volumes of *water* and 1 volume of *glacial acetic acid* as the mobile phase with a flow rate of 2 mL per minute and (c) a detection wavelength of 263 nm.

Calculate the content of $C_{10}H_{15}NO$,HCl in the nasal drops using the declared content of $C_{10}H_{15}NO$,HCl in *ephedrine hydrochloride BPCRS*.

When ephedrine nasal drops are prescribed or demanded no strength being stated, nasal drops containing 0.5% w/v of ephedrine hydrochloride shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

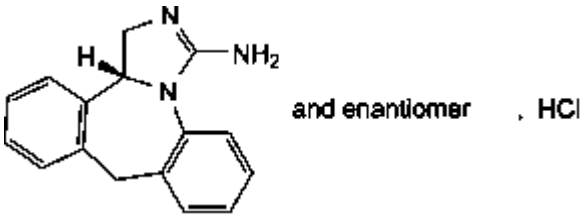
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Epinastine Hydrochloride

General Notices

(Ph. Eur. monograph 2411)



$C_{16}H_{16}ClN_3$ 285.8 *108929-04-0*

Action and use

Antihistamine.

Ph Eur

DEFINITION

(13b*RS*)-9,13b-Dihydro-1*H*-dibenzo[*c,f*]imidazo[1,5-*a*]azepin-3-amine hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water and in methanol, sparingly soluble in methylene chloride, slightly soluble in acetonitrile.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *epinastine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acidity or alkalinity

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Add 0.1 mL of *methyl red mixed solution R* and 0.25 mL of *0.01 M sodium hydroxide*. The solution is green. Add 0.5 mL of *0.01 M hydrochloric acid*. The solution is reddish-violet.

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution pH 4.4 Dissolve 3.8 g of *sodium pentanesulfonate monohydrate R* and 4.0 g of *potassium dihydrogen phosphate R* in 900 mL of *water for chromatography R*, adjust to pH 4.4 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Solvent mixture Mobile phase B, mobile phase A (25:75 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *epinastine for system suitability A CRS* (containing impurity A) in 10 mL of the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 3.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase :

— *mobile phase A*: *methanol R1*, buffer solution pH 4.4 (15:85 *V/V*);

— *mobile phase B*: *methanol R1*, *acetonitrile for chromatography R* (15:85 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	80	20
4 - 13	80 → 30	20 → 70

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *epinastine for system suitability A CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to epinastine (retention time = about 4 min): impurity A = about 1.2.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to epinastine.

Calculation of percentage contents:

— for each impurity, use the concentration of epinastine hydrochloride in reference solution (a).

Limits:

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.7 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 100 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 2 volumes of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 28.58 mg of $C_{16}H_{16}ClN_3$.

STORAGE

In an airtight container.

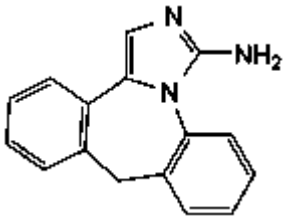
IMPURITIES

Specified impurities *A.*

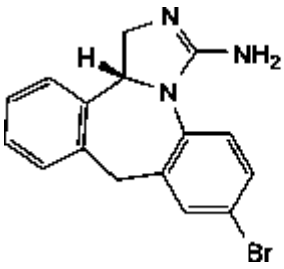
www.webofpharma.com

https://thuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. 9*H*-dibenzo[*c,f*]imidazo[1,5-*a*]azepin-3-amine,



and enantiomer

B. (13b*RS*)-7-bromo-9,13b-dihydro-1*H*-dibenzo[*c,f*]imidazo[1,5-*a*]azepin-3-amine.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

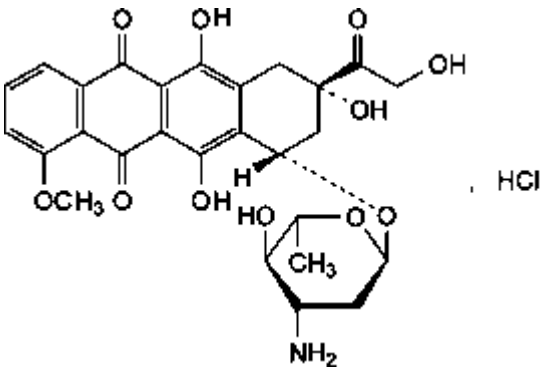
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Epirubicin Hydrochloride

General Notices

(Ph. Eur. monograph 1590)



$C_{27}H_{30}ClNO_{11}$ 580.0 *56390-09-1*

Action and use

Cytotoxic.

Preparation

Epirubicin Injection

Ph Eur

DEFINITION

(8*S*,10*S*)-10-[(3-Amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride.

Semi-synthetic product derived from a fermentation product.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Orange-red powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Soluble in water and in methanol, slightly soluble in anhydrous ethanol, practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *epirubicin hydrochloride CRS*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

C. Dissolve about 10 mg in 0.5 mL of *nitric acid R*, add 0.5 mL of *water R* and heat over a flame for 2 min. Allow to cool and add 0.5 mL of *silver nitrate solution R1*. A white precipitate is formed.

TESTS

pH (*2.2.3*)

4.0 to 5.5.

Dissolve 50 mg in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Allow the solutions to stand for 3 h before use.*

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *epirubicin hydrochloride CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *epirubicin hydrochloride CRS* and 10 mg of *doxorubicin hydrochloride CRS* (impurity C) in the mobile phase and dilute to 100 mL with the mobile phase.

Reference solution (c) In order to prepare impurity A *in situ*, dissolve 10 mg of *doxorubicin hydrochloride CRS* in a mixture of 5 mL of *phosphoric acid R* and 5 mL of *water R*. Allow to stand for 30 min. Adjust to pH 2.6 with an 80 g/L solution of *sodium hydroxide R*. Add 10 mL of *methanol R* and 15 mL of *acetonitrile R*. Mix.

Reference solution (d) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *trimethylsilyl silica gel for chromatography R* (5 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 35 °C.

Mobile phase Mix 17 volumes of *methanol R*, 29 volumes of *acetonitrile R* and 54 volumes of a solution containing 3.7 g/L of *sodium laurilsulfate R* and 2.8 per cent *V/V* of *dilute phosphoric acid R*.

Flow rate 2.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Run time 3.5 times the retention time of epirubicin.

Identification of impurities Use the 2nd most abundant peak present in the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to epirubicin (retention time = about 9.5 min): impurity A = about 0.3; impurity C = about 0.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity C and epirubicin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.7;

— *impurities A, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (1.0 per cent);

— *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (2.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent).

Acetone (*2.4.24*)

Maximum 1.5 per cent.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.100 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Calculate the percentage content of $C_{27}H_{30}ClNO_{11}$ taking into account the assigned content of *epirubicin hydrochloride CRS*.

STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

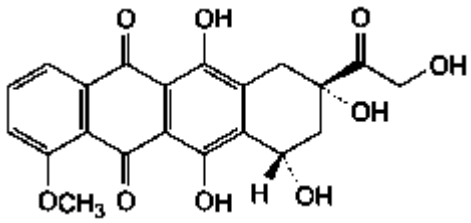
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

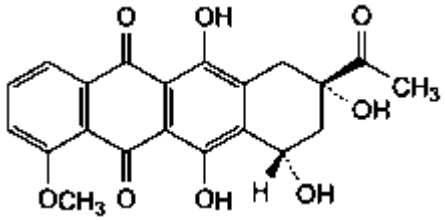
IMPURITIES

Specified impurities *A, C.*

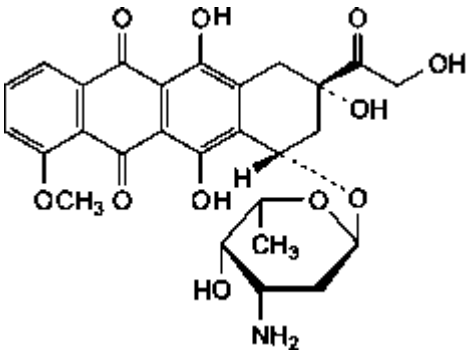
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E, F, G.*



A. (8*S*,10*S*)-6,8,10,11-tetrahydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (doxorubicinone),



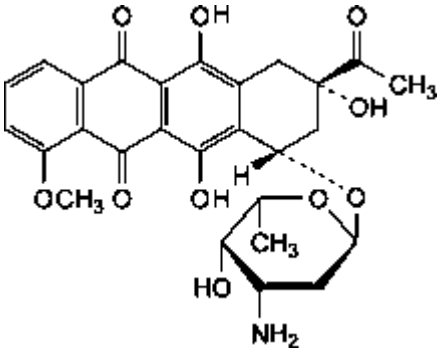
B. (8*S*,10*S*)-8-acetyl-6,8,10,11-tetrahydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (daunorubicinone),



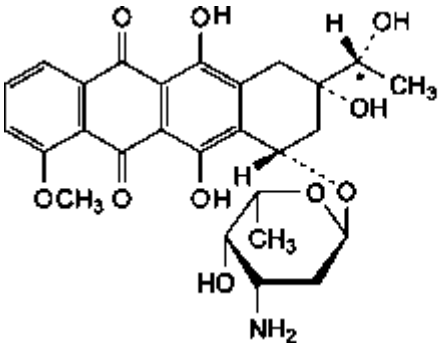
www.webofpharma.com

https://thuocngocanh.com/

C. (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (doxorubicin),

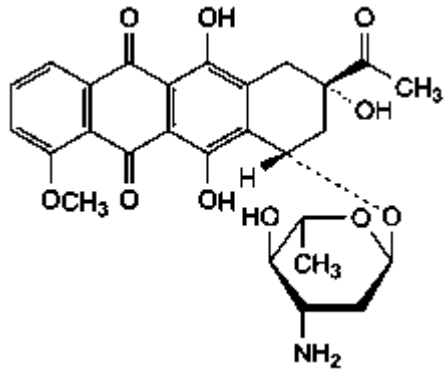


D. (8*S*,10*S*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (daunorubicin),



and epimer at C*

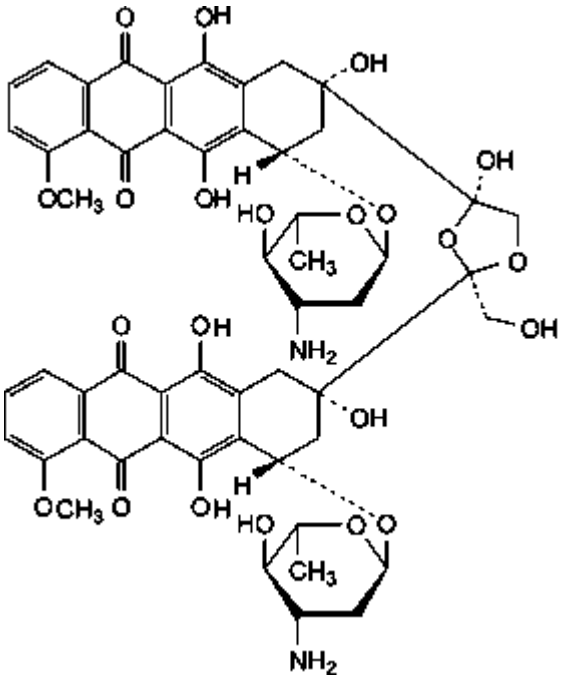
E. (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-[(1*RS*)-1-hydroxyethyl]-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (dihydrodaunorubicin),



F. (8*S*,10*S*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione (*epi*-daunorubicin),

www.webofpharma.com

https://thuocngocanh.com/



G. 8,8′-[(2*R*,4*R*)-4-hydroxy-2-(hydroxymethyl)-1,3-dioxolane-2,4-diyl]bis[(8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione] (epirubicin dimer).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Epirubicin Injection

General Notices

Action and use

Anthracycline antibacterial; cytostatic.

DEFINITION

Epirubicin Injection is a sterile solution of Epirubicin Hydrochloride in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of epirubicin hydrochloride, $C_{27}H_{29}NO_{11},HCl$

95.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dilute a volume of the injection containing 10 mg of Epirubicin Hydrochloride to 100 mL with *water* and further dilute 5 mL to 50 mL with *water*. The *light absorption* of the resulting solution, Appendix II B, in the range 220 to 350 nm exhibits three maxima at 233, 253 and 292 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.5 to 4.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Allow the solutions to stand for 3 hours before use.

(1) Dilute a volume of the injection with sufficient of the mobile phase to produce a solution containing 0.1% w/v of Epirubicin Hydrochloride.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 0.01% w/v of each of *doxorubicin hydrochloride BPCRS* and *epirubicin hydrochloride BPCRS* in the mobile phase.

(4) Dissolve 10 mg of *doxorubicin hydrochloride BPCRS* in a mixture of 5 mL of *water* and 5 mL of *orthophosphoric acid* and allow to stand for 30 minutes. Adjust the pH of the solution to 2.6 with an 8% w/v solution of s*odium hydroxide*, add 15 mL of *acetonitrile* and 10 mL

www.webofpharma.com

https://thuocngocanh.com/

of *methanol* and mix (generation of impurity A).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *trimethylsilyl silica gel for chromatography* (6 µm) (Zorbax TMS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3.5 times the retention time of epirubicin.

MOBILE PHASE

17 volumes of *methanol*, 29 volumes of *acetonitrile* and 54 volumes of a solution containing 0.37% w/v of *sodium dodecyl sulfate* and 2.8% v/v of 1M *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to epirubicin (retention time about 9.5 minutes) are: impurity A, about 0.3; impurity B, about 0.4; impurity C, about 0.8; impurity E, about 1.1; impurity D, about 1.5; impurity F, about 1.7; impurity G, about 2.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to doxorubicin and epirubicin is at least 2.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) corresponding to impurity A using the second most abundant peak in the chromatogram obtained with solution (4) and multiply the area of this peak by the corresponding correction factor: 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A (doxorubicin aglycone, doxorubicinone), is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the area of any peak corresponding to impurity C (doxorubicin) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all the *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (4%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Bacterial endotoxins

www.webofpharma.com

https://thuocngocanh.com/

Carry out the test for *bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, with *water BET* to give a solution containing 2 mg per mL of Epirubicin Hydrochloride (solution A). The endotoxin limit concentration of solution A is not more than 2.2 IU per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Allow the solutions to stand for 3 hours before use.

(1) Dilute a volume of the injection with sufficient of the mobile phase to produce a solution containing 0.1% w/v of Epirubicin Hydrochloride.

(2) 0.1% w/v of *epirubicin hydrochloride BPCRS* in the mobile phase.

(3) 0.01% w/v of each of *doxorubicin hydrochloride BPCRS* and *epirubicin hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *trimethylsilyl silica gel for chromatography* (6 µm) (Zorbax TMS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

17 volumes of *methanol*, 29 volumes of *acetonitrile* and 54 volumes of a solution containing 0.37% w/v of *sodium dodecyl sulfate* and 2.8% v/v of 1M *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to doxorubicin and epirubicin is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{27}H_{29}NO_{11}$,HCl in the injection using the declared content of $C_{27}H_{29}NO_{11}$,HCl in *epirubicin hydrochloride BPCRS*.

STORAGE

Epirubicin Injection should be stored at a temperature of 2° to 8°.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Epirubicin Hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

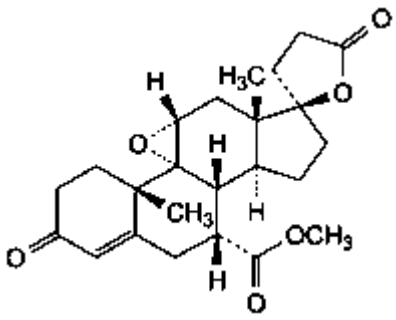
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Eplerenone

General Notices

(Ph. Eur. monograph 2765)



$C_{24}H_{30}O_6$ 414.5 *107724-20-9*

Action and use

Aldosterone receptor antagonist; antihypertensive.

Preparation

Eplerenone Tablets

Ph Eur

DEFINITION

9,11α-Epoxy-7α-(methoxycarbonyl)-3-oxo-17α-pregn-4-ene-21,17-carbolactone.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White, almost white or slightly yellow, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *eplerenone CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Specific optical rotation (2.2.7)

-16.0 to -14.0.

Dissolve 0.250 g in *acetonitrile R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *methanol R*, *water R* (25:25:50 *V/V/V*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *eplerenone for system suitability CRS* (containing impurities A and D) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *eplerenone for peak identification CRS* (containing impurity B) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 25.0 mg of *eplerenone CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 30 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *phosphoric acid R*, *acetonitrile R*, *methanol R* (0.1:40:60 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	54	46
25 - 32	54 → 40	46 → 60
32 - 45	40	60

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *eplerenone for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and D; use the chromatogram supplied with *eplerenone for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to eplerenone (retention time = about 9 min): impurity D = about 0.71; impurity A = about 0.74; impurity B = about 1.2.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of eplerenone in reference solution (c).

Limits:

— *impurities A, B*: for each impurity, maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

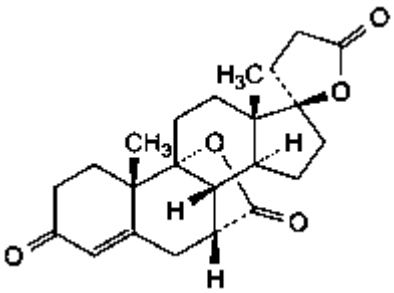
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{24}H_{30}O_6$ taking into account the assigned content of *eplerenone CRS*.

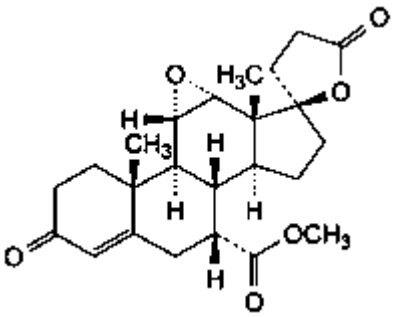
IMPURITIES

Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F, G.*



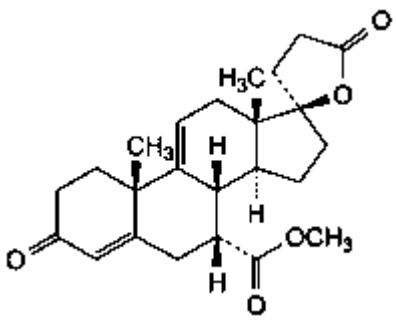
A. 3-oxo-17α-pregn-4-ene-7α,9:21,17-dicarbolactone,



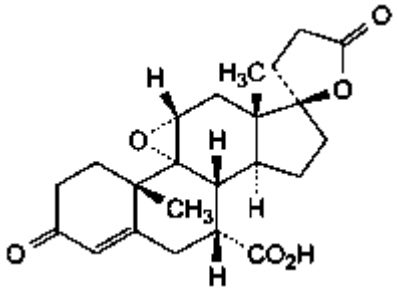
B. 11α,12α-epoxy-7α-(methoxycarbonyl)-3-oxo-17α-pregn-4-ene-21,17-carbolactone,

www.webofpharma.com

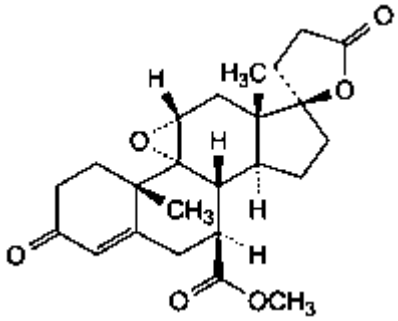
https://thuocngocanh.com/



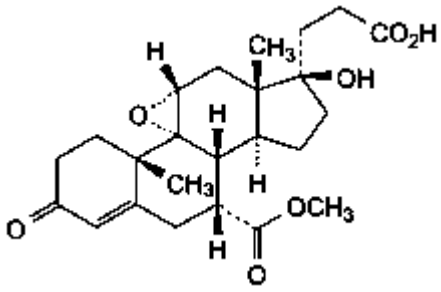
C. 7α-(methoxycarbonyl)-3-oxo-17α-pregna-4,9(11)-diene-21,17-carbolactone,



D. (2′*R*)-9,11α-epoxy-3,5′-dioxo-4′,5′-dihydro-3′*H*-spiro[androst-4-ene-17,2′-furan]-7α-carboxylic acid,



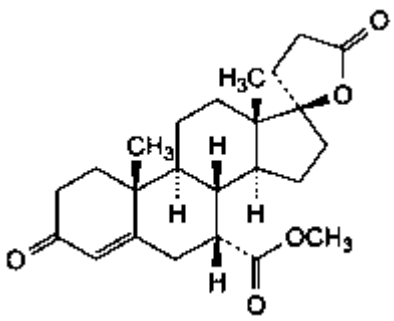
E. 9,11α-epoxy-7β-(methoxycarbonyl)-3-oxo-17α-pregn-4-ene-21,17-carbolactone,



F. 9,11α-epoxy-17-hydroxy-7α-(methoxycarbonyl)-3-oxo-17α-pregn-4-ene-21-carboxylic acid,

www.webofpharma.com

https://thuvienthuocngocanh.com/



G. 7α-(methoxycarbonyl)-3-oxo-17α-pregn-4-ene-21,17-carbolactone.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Eplerenone Tablets

General Notices

Action and use

Aldosterone receptor antagonist; antihypertensive.

DEFINITION

Eplerenone Tablets contain Eplerenone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of eplerenone, $C_{24}H_{30}O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of powdered tablets containing 50 mg of Eplerenone with 25 mL of *dichloromethane* and filter. Evaporate the filtrate to dryness on a *water-bath*. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectra of *eplerenone EPCRS* which has been treated in the same manner.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 1% w/v *sodium dodecyl sulfate* in 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B 25 volumes of *acetonitrile*, 25 volumes of *methanol* and 50 volumes of *water*.

(1) After 30 minutes withdraw a sample of the medium and filter. Dilute the filtrate, if necessary, with 0.1M *hydrochloric acid* to produce a solution expected to contain 0.0028% w/v of Eplerenone.

(2) 0.0028% w/v of *eplerenone EPCRS* in 0.1M *hydrochloric acid*.

(3) 0.025% w/v of *eplerenone for system suitability EPCRS* in Solution B.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thietbiuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

Solution A 0.1 volume of *orthophophoric acid*, 40 volumes of *acetonitrile* and 60 volumes of *methanol*

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm) (Inertsil ODS-3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

46 volumes of solution A and 54 volumes of a 0.1% v/v solution of *orthophophoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to eplerenone (retention time about 9.3 minutes) are: impurity D, about 0.71 and impurity A, about 0.74.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity A is at least 5.0.

DETERMINATION OF CONTENT

Calculate the total content of eplerenone, $C_{24}H_{30}O_6$, in the medium from the chromatograms obtained and using the declared content of $C_{24}H_{30}O_6$ in *eplerenone EPCRS*.

LIMITS

The amount of eplerenone released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 25 mg of Eplerenone with 40 mL of solution B, add sufficient solution B to produce 50mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with Solution B. Further dilute 1 volume of this solution to 5 volumes with the same solvent.

(3) 0.05% w/v of *eplerenone for system suitability EPCRS* in Solution B.

(4) 0.05% w/v of *eplerenone for peak identification EPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm) (Inertsil ODS-3 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1% v/v solution of *orthophophoric acid*.

Mobile phase B 0.1 volumes of *orthophophoric acid*, 40 volumes of *acetonitrile* and 60 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-25	54	46	isocratic
25-32	54→40	46→60	linear gradient
32-45	40	60	isocratic
45-46	40→54	60→46	linear gradient
46-55	54	46	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to eplerenone (retention time about 9 minutes) are: impurity D, about 0.71; impurity A, about 0.74 and impurity B, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless:

In the chromatogram obtained with solution (3):

the *peak-to-valley ratio* is at least 4.0, where *Hp* is the height above the baseline of the peak due to impurity A and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity D;

LIMITS

Identify any peak corresponding to impurities A and D in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and any peak corresponding to impurity B using the chromatogram obtained with solution (4).

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity A or impurity B is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1%).

www.webofpharma.com

https://thuocngocanh.com/

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B 25 volumes of *acetonitrile*, 25 volumes of *methanol* and 50 volumes of *water*.

(1) Shake a quantity of powdered tablets containing 25 mg of Eplerenone with 40 mL of Solution B, add sufficient Solution B to produce 50mL and filter. Dilute 1 volume of the filtrate to 10 volumes with Solution B.

(2) 0.005% w/v of *eplerenone EPCRS* in Solution B.

(3) 0.05% w/v of *eplerenone for system suitability EPCRS* in Solution B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity A is at least 5.0.

DETERMINATION OF CONTENT

Calculate the content of eplerenone, $C_{24}H_{30}O_6$, in the tablets from the chromatograms obtained and using the declared content of $C_{24}H_{30}O_6$, in *eplerenone EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Eplerenone.

© Crown Copyright 2022

www.webofpharma.com

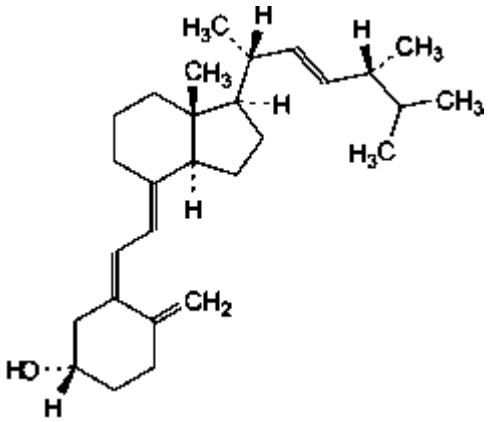
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ergocalciferol

General Notices

(Ph. Eur. monograph 0082)



$C_{28}H_{44}O$ 396.7 *50-14-6*

Action and use

Vitamin D analogue (Vitamin D_2).

Preparations

Calcium and Ergocalciferol Tablets

Calcium and Ergocalciferol Chewable Tablets

Ergocalciferol Injection

Ergocalciferol Tablets

When vitamin D_2 is prescribed or demanded, Ergocalciferol shall be dispensed or supplied. When calciferol or vitamin D is prescribed or demanded, Ergocalciferol or Colecalciferol shall be dispensed or supplied.

Ph Eur

DEFINITION

(3*S*,5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraen-3-ol.

Content

www.webofpharma.com

https://thuocngocanh.com/

97.0 per cent to 102.0 per cent.

A suitable antioxidant may be added.

A reversible isomerisation to pre-ergocalciferol takes place in solution, depending on temperature and time. The activity is due to both compounds (see Assay).

1 mg of ergocalciferol is equivalent to 40 000 IU of antirachitic activity (vitamin D) in rats.

CHARACTERS

Appearance

White or slightly yellowish, crystalline powder or white or almost white crystals.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent) and in methanol, soluble in fatty oils.

It is sensitive to air, heat and light.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *ergocalciferol CRS*.

TESTS

Specific optical rotation (2.2.7)

+ 103 to + 107.

Dissolve 0.200 g rapidly and without heating in *aldehyde-free alcohol R* and dilute to 25.0 mL with the same solvent. Examine within 30 min of preparing the solution.

Reducing substances

Dissolve 0.1 g in *aldehyde-free alcohol R* and dilute to 10.0 mL with the same solvent. Add 0.5 mL of a 5 g/L solution of *tetrazolium blue R* in *aldehyde-free alcohol R* and 0.5 mL of *dilute tetramethylammonium hydroxide solution R*. Allow to stand for exactly 5 min and add 1.0 mL of *glacial acetic acid R*. Prepare a reference solution at the same time and in the same manner using 10.0 mL of a solution containing 0.2 µg/mL of *hydroquinone R* in *aldehyde-free alcohol R*. Measure the absorbance (2.2.25) of the 2 solutions at 525 nm using as the compensation liquid 10.0 mL of *aldehyde-free alcohol R* treated in the same manner. The absorbance of the test solution is not greater than that of the reference solution (20 ppm).

Impurity B

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use, avoiding exposure to actinic light and air.*

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 25.0 mg of the substance to be examined without heating in *methanol R* and dilute to 25.0 mL with the same solvent.

Reference solution Dissolve 5.0 mg of *ergosterol CRS* (impurity B) without heating in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase *methanol R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 282 nm.

Injection 20 µL.

Run time 2.5 times the retention time of ergocalciferol.

Relative retention With reference to ergocalciferol (retention time = about 7 min): impurity B = about 1.6.

Limit:

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use, avoiding exposure to actinic light and air.*

Test solution Dissolve 15.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *ergocalciferol for system suitability CRS* (containing impurities A, F and G) in 10 mL of the mobile phase. Heat in a water-bath at 90 °C under a reflux-condenser for 45 min and allow to cool (*in-situ* degradation to obtain pre-ergocalciferol). Dilute 3 mL of the solution to 25 mL with the mobile phase.

Reference solution (b) Dissolve 15.0 mg of *ergocalciferol CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of reference solution (c) to 10.0 mL with the mobile phase.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase *methanol R*, *acetonitrile R* (10:90 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 20 µL of the test solution and reference solutions (a), (c) and (d).

Run time Twice the retention time of ergocalciferol.

Identification of impurities Use the chromatogram supplied with *ergocalciferol for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, F and G, and pre-ergocalciferol.

Relative retention With reference to ergocalciferol (retention time = about 13 min): impurity F = about 0.6; impurity A = about 0.8; pre-ergocalciferol = about 0.9; impurity G = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity A and pre-ergocalciferol; minimum 2.5 between the peaks due to pre-ergocalciferol and ergocalciferol.

Calculation of percentage contents:

— for impurities A, F and G, use the concentration of ergocalciferol in reference solution (c);

— for impurities other than A, F and G, use the concentration of ergocalciferol in reference solution (d).

Limits:

— *impurity G*: maximum 1.5 per cent;

— *impurities A, F*: for each impurity, maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak due to pre-ergocalciferol or the antioxidant.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (b).

www.webofpharma.com

https://thuocngocanh.com/

Calculate the percentage content of $C_{28}H_{44}O$ taking into account the assigned content of *ergocalciferol CRS*, and if present, the peak due to pre-ergocalciferol in the test solution.

STORAGE

Under an inert gas, in an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

The contents of an opened container are to be used immediately.

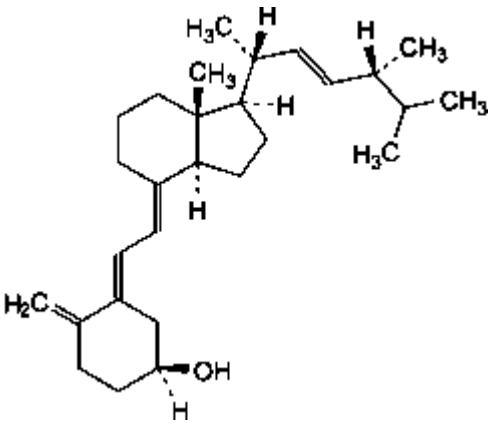
LABELLING

The label states the name and concentration of any added antioxidant.

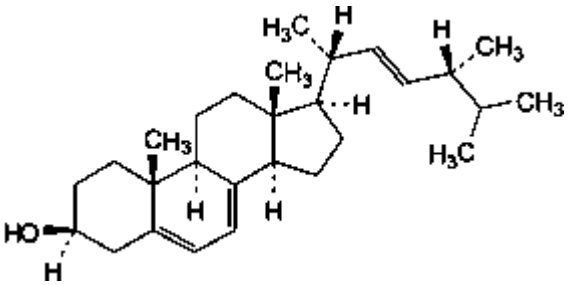
IMPURITIES

Specified impurities *A, B, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E.*



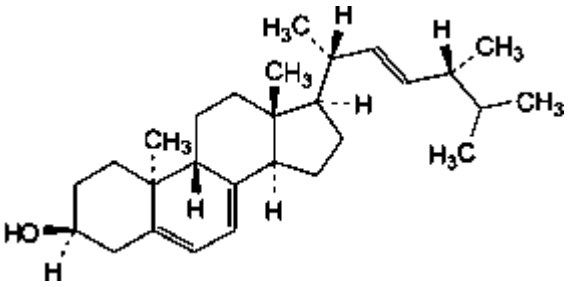
A. (3*S*,5*E*,7*E*,22*E*)-9,10-secoergosta-5,7,10(19),22-tetraen-3-ol (*trans*-vitamin D_2),



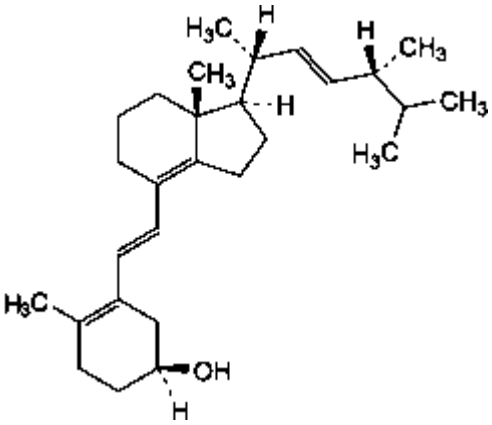
B. (22*E*)-ergosta-5,7,22-trien-3β-ol (ergosterol),

www.webofpharma.com

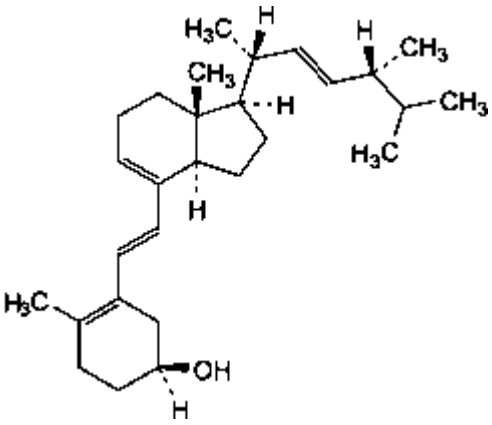
https://thuvienthuocngocanh.com/



C. (22*E*)-9β,10α-ergosta-5,7,22-trien-3β-ol (lumisterol$_2$),



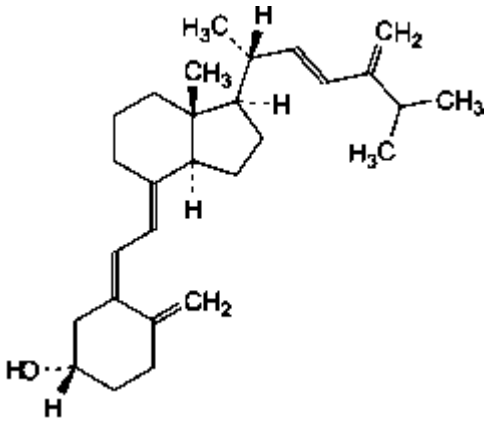
D. (3*S*,6*E*,22*E*)-9,10-secoergosta-5(10),6,8(14),22-tetraen-3-ol (iso-tachysterol$_2$),



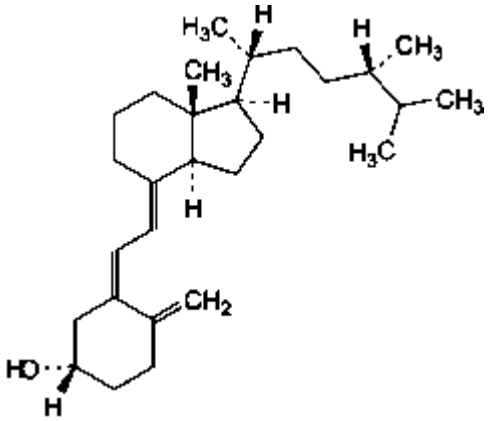
E. (3*S*,6*E*,22*E*)-9,10-secoergosta-5(10),6,8,22-tetraen-3-ol (tachysterol$_2$),

www.webofpharma.com

https://thuocngocanh.com/



F. (3*S*,5*Z*,7*E*,22*E*)-9,10-secoergosta-5,7,10(19),22,24(24^1)-pentaen-3-ol,



G. (3*S*,5*Z*,7*E*)-9,10-secoergosta-5,7,10(19)-trien-3-ol (vitamin D_4).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ergocalciferol Injection

General Notices

Action and use

Vitamin D analogue (Vitamin D_2).

DEFINITION

Ergocalciferol Injection is a sterile solution of Ergocalciferol in Ethyl Oleate.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of ergocalciferol, $C_{28}H_{44}O$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless to pale yellow, oily liquid.

IDENTIFICATION

To 1 mL of a 0.2% v/v solution of the injection in *ethanol-free chloroform* add 9 mL of *antimony trichloride solution*. The *light absorption* of the resulting solution, Appendix II B, exhibits a maximum at 500 nm.

ASSAY

Carry out the following procedure in subdued light. Dilute 0.1 g of the injection to 50 mL with dry *1,2-dichloroethane* that has been purified by passing it through a column of *silica gel*. To 1 mL of this solution add rapidly 9 mL of *antimony trichloride in dichloroethane solution* and measure the *absorbance* of the solution at 500 and 550 nm, Appendix II B, 90 to 120 seconds after adding the reagent. Repeat the operation using 1 mL of a 0.002% w/v solution of *ergocalciferol BPCRS* in the dry, purified 1,2-dichloroethane, beginning at the words ‘add rapidly 9 mL of *antimony trichloride solution*…’. Calculate the result of the assay from the difference between the absorbances at 500 and 550 nm and using the declared content of $C_{28}H_{44}O$ in *ergocalciferol BPCRS*. Calculate the percentage w/v of ergocalciferol taking 0.87 g as the value of the weight per mL of the injection.

STORAGE

Ergocalciferol Injection should be protected from light.

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The label states (1) that the preparation is for intramuscular use only; (2) the equivalent number of IU (units) of antirachitic activity (vitamin D) in 1 mL.

Each µg of ergocalciferol is equivalent to 40 IU of antirachitic activity (vitamin D).

When calciferol injection is prescribed or demanded, Colecalciferol Injection or Ergocalciferol Injection shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ergocalciferol Tablets

General Notices

Action and use

Vitamin D analogue (Vitamin D_2).

DEFINITION

Ergocalciferol Tablets contain Ergocalciferol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ergocalciferol, $C_{28}H_{44}O$

90.0 to 125.0% of the stated amount.

IDENTIFICATION

A. In the test for Uniformity of content, the chromatogram obtained with solution (2) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (1).

B. Extract one powdered tablet with 5 mL of *dichloromethane*, filter and to 1 mL of the filtrate add 9 mL of *antimony trichloride solution*. A brownish red colour is produced.

TESTS

Uniformity of content

Ergocalciferol Tablets comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) 0.001% w/v of *ergocalciferol BPCRS* in *hexane*.

(2) For tablets containing more than 0.25 mg of ergocalciferol prepare the solution in the following manner. Add 4 mL of *water* to one tablet in an amber flask and disperse with the aid of ultrasound. Add 12 mL of *dimethyl sulfoxide*, mix, extract with 100 mL of *hexane* by shaking for 30 minutes, centrifuge the hexane layer and use the clear supernatant liquid.
For tablets containing 0.25 mg or less carry out the same procedure but using 2 mL of *water*, 6 mL of *dimethyl sulfoxide* and 25 mL of *hexane*.

(3) Dissolve 0.5 mL of *cholecalciferol for system suitability EPCRS* in 2 mL of *toluene* and dilute to 10 mL with the mobile phase; heat under a reflux condenser in a water bath at 90° for 45 minutes and cool.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *silica gel for chromatography* (5 µm) (Partisil is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

8 volumes of *pentan-1-ol* and 992 volumes of *hexane*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to precolecalciferol and *trans*-colecalciferol is at least 1.0.

DETERMINATION OF CONTENT

Calculate the content of ergocalciferol, $C_{28}H_{44}O$, in each tablet using the declared content of $C_{28}H_{44}O$ in *ergocalciferol BPCRS*.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of content.

LABELLING

The label states the equivalent number of IU (International Units) of antirachitic activity (vitamin D) per tablet.

Each µg of ergocalciferol is equivalent to 40 IU of antirachitic activity (vitamin D).

When calciferol tablets are prescribed or demanded, Colecalciferol Tablets or Ergocalciferol Tablets shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ergometrine and Oxytocin Injection

General Notices

Action and use

Oxytocic.

DEFINITION

Ergometrine and Oxytocin Injection is a sterile solution containing Ergometrine Maleate and either Oxytocin or Oxytocin Concentrated Solution in Water for Injections containing maleic acid.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of ergometrine maleate, $C_{19}H_{23}N_3O_2,C_4H_4O_4$

90.0 to 110.0% of the stated amount.

Content of oxytocin, $C_{43}H_{66}N_{12}O_{12}S_2$

90.0 to 105.0% of the stated amount.

By convention, for the purpose of labelling oxytocin preparations, 1 mg of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) is equivalent to 600 IU of biological activity.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. In the Related substances test for ergometrine maleate, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. To a volume containing 0.1 mg of Ergometrine Maleate, add 0.5 mL of *water* and 2 mL of *dimethylaminobenzaldehyde solution R6*. After about 5 minutes a deep blue colour is produced.

C. In the Assay for oxytocin the peak in the chromatogram obtained with solution (2) corresponds to the peak due to oxytocin in the chromatogram obtained with solution (1).

TESTS

Acidity

www.webofpharma.com

https://thuocngocanh.com/

pH, 2.9 to 3.5, Appendix V L.

Related substances

For ergometrine maleate

Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions prepared immediately before use, *protected from light*.

(1) Add 10 mL of absolute ethanol to a volume of the injection containing 0.5 mg of Ergometrine Maleate and evaporate to dryness at a temperature not exceeding 30° at a pressure of 2 kPa; to the residue add 0.2 mL of a mixture of 1 volume of 13.5M ammonia and 9 volumes of ethanol (80%), mix, centrifuge and use the supernatant liquid.
(2) 0.250% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).
(3) 0.0250% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).
(4) 0.0125% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).
(5) 0.0050% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).
(6) 0.00250% w/v of *ergometrine maleate BPCRS* respectively in a mixture of 1 volume of 3.5M ammonia and 9 volumes of ethanol (80%).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.
(d) Develop the plate to 14 cm.
(e) After removal of the plate, dry it in a current of cold air, spray with *dimethylaminobenzaldehyde solution R7* and dry the plate at 105° for 2 minutes.

MOBILE PHASE

75 volumes of *chloroform*, 25 volumes of *methanol* and 3 volumes of *water*.

CONFIRMATION

Assess the intensities of any secondary spots in the chromatogram obtained with solution (1) by reference to the spots in the chromatograms obtained with solutions (3) to (6), making allowance for area in assessing the intensities of spots of different Rf values. The sum of the intensities so assessed does not exceed 10% of the intensity of the principal spot.

For oxytocin

Carry out the method for liquid chromatography, Appendix III D using the following solutions prepared immediately before use, *protected from light*.

(1) Dilute the injection, if necessary, with *water* to give a solution containing the equivalent of 0.00083% w/v oxytocin.
(2) Prepare a 0.00083% w/v *oxytocin EPCRS* in a 0.1M *sodium dihydrogen orthophosphate* solution.
(3) Dilute 2.5 volumes of solution (2) to 100 volumes with *water*.
(4) To 900 µL of solution (2) add 100 µL of 1M *hydrochloric acid* and heat at approximately 100° for 10 minutes for in situ generation of oxytocin impurity 1.

www.webofpharma.com

https://thuocngocanh.com/

(5) Dilute 2 volumes of solution (3) to 25 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography R1* (3 µm) (Nucleosil is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use detection wavelengths of 220 nm and 320 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1M *sodium dihydrogen orthophosphate*.

Mobile phase B 1 volume of *acetonitrile* and 1 volume of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	69	31	isocratic
3-20	69→57	31→43	linear gradient
20-22	57	43	isocratic
22-22.1	57→69	43→31	linear gradient
22.1-28	69	31	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to oxytocin (retention time about 10 minutes) is: impurity 1, about 0.9.

SYSTEM SUITABILITY

At 220 nm

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peaks due to oxytocin and impurity 1 is at least 1.5.

LIMITS

At 220 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than three times the area of the principal peak in the chromatogram obtained with solution (3) (7.5%);

the area of any *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (3) (1%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of all the secondary peaks is not greater than 3.8 times the area of the principal peak in the chromatogram obtained with solution (3) (9.5%);

disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%) and any peak that is visible at 320 nm.

ASSAY

For ergometrine maleate

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared immediately before use, *protected from light*.

(1) Dilute the injection, if necessary, with water to give a solution containing the equivalent of 0.05% w/v ergometrine maleate.
(2) 0.05% w/v of *ergometrine maleate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 320 nm.

MOBILE PHASE

92 volumes of a 0.2% v/v solution of *orthophosphoric acid* and 8 volumes of *acetonitrile*.

Calculate the content of $C_{19}H_{23}N_3O_2,C_4H_4O_4$ from the declared content of $C_{19}H_{23}N_3O_2,C_4H_4O_4$ in *ergometrine maleate BPCRS*.

For oxytocin

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared immediately before use, *protected from light*.

(1) Dilute the injection, if necessary, with *water* to give a solution containing the equivalent of 0.00083% w/v of oxytocin.
(2) 0.00083% w/v *oxytocin EPCRS* in 0.1M *sodium dihydrogen orthophosphate* solution.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography R1* (3 µm) (Nucleosil is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use detection wavelength of 220 nm.
(f) Inject 200 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

Mobile phase A 0.1M *sodium dihydrogen orthophosphate*.

Mobile phase B 1 volume of *acetonitrile* and 1 volume of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-35	76	24	isocratic
35-40	76→20	24→80	linear gradient
40-45	20	80	isocratic
45-45.1	20→76	80→24	linear gradient
45.1-50	76	24	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (1), the peak due oxytocin elutes between 23 and 35 minutes

DETERMINATION OF CONTENT

Calculate the content of $C_{43}H_{66}N_{12}O_{12}S_2$ from the declared content in *oxytocin EPCRS*.

STORAGE

Ergometrine and Oxytocin Injection should be protected from light and stored at a temperature of 2° to 8°.

LABELLING

The strength with respect to oxytocin is stated as the number of IU (units) per mL. The label also states the equivalent number of µg of oxytocin per mL.

IMPURITIES

The impurities limited by the requirements of this monograph include:

1. Oxytocin impurity 1, unknown structure.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ergometrine Injection

General Notices

Action and use

Oxytocic.

DEFINITION

Ergometrine Injection is a sterile solution of Ergometrine Maleate in Water for Injections. The acidity of the solution is adjusted to pH 3 by the addition of maleic acid.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of ergometrine maleate, $C_{19}H_{23}N_3O_2,C_4H_4O_4$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless or faintly yellow solution.

IDENTIFICATION

A. In the test for Related substances, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (5).

B. Exhibits a blue fluorescence.

C. To a volume containing 0.1 mg of Ergometrine Maleate, add 0.5 mL of *water* and 2 mL of *dimethylaminobenzaldehyde solution R6*. A deep blue colour is produced after about 5 minutes.

TESTS

Acidity

pH, 2.7 to 3.5, Appendix V L.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, in subdued light, using the following solutions in *methanol*. Protect from light any solutions not used immediately.

(1) Evaporate a volume of the injection containing 1 mg of Ergometrine Maleate to dryness at 20° at a pressure of 2 kPa and dissolve the residue in 0.25 mL.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.010% w/v of *ergometrine maleate BPCRS*.

(3) 0.020% w/v of *ergometrine maleate BPCRS*.

(4) 0.040% w/v of *ergometrine maleate BPCRS*.

(5) 0.40% w/v of *ergometrine maleate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a suspension of *silica gel G* in 0.1M *sodium hydroxide* to prepare the plate.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of *chloroform*.

LIMITS

Assess the intensities of any *secondary spots* in the chromatogram obtained with solution (1) by reference to the spots in the chromatograms obtained with solutions (2), (3) and (4). The total of the intensities so assessed does not exceed 10% of the intensity of the principal spot.

ASSAY

Carry out the following procedure protected from light using the following two solutions prepared at the same time.

(1) Dilute a suitable volume with sufficient *water* to produce a solution containing 0.004% w/v of Ergometrine Maleate. To 3 mL add 6 mL of *dimethylaminobenzaldehyde solution R6*, mix, cool to room temperature and allow to stand for 30 minutes.

(2) To 3 mL of a 0.004% w/v solution of *ergometrine maleate BPCRS* add 6 mL of *dimethylaminobenzaldehyde solution R6*, mix, cool to room temperature and allow to stand for 30 minutes.

Measure the *absorbance* of solution (2) at the maximum at 545 nm, Appendix II B, using in the reference cell a solution prepared by mixing 6 mL of *dimethylaminobenzaldehyde solution R6* and 3 mL of *water*. Without delay replace solution (2) with solution (1), using the same cell, and measure the *absorbance* of solution (1) at the same wavelength. Calculate the content of $C_{19}H_{23}N_3O_2,C_4H_4O_4$ using the declared content of $C_{19}H_{23}N_3O_2,C_4H_4O_4$ in *ergometrine maleate BPCRS*.

STORAGE

Ergometrine Injection should be protected from light and stored at a temperature of 2° to 8°.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

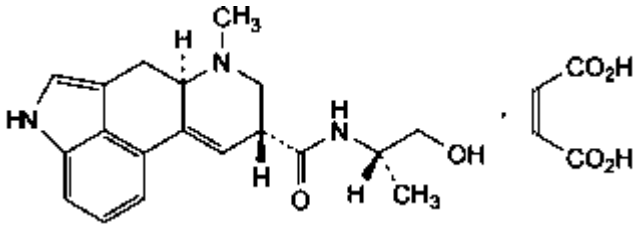
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ergometrine Maleate

General Notices

(Ph. Eur. monograph 0223)



$C_{23}H_{27}N_3O_6$ 441.5 *129-51-1*

Action and use

Oxytocic.

Preparations

Ergometrine Injection

Ergometrine and Oxytocin Injection

Ph Eur

DEFINITION

(8β)-*N*-[(2*S*)-1-Hydroxypropan-2-yl]-6-methyl-9,10-didehydroergoline-8-carboxamide (2*Z*)-but-2-enedioate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white or slightly coloured, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

https://thuocngocanh.com/

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ergometrine maleate CRS*.

B. Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use.*

Solvent mixture *concentrated ammonia R*, *ethanol (80 per cent V/V) R* (10:90 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution Dissolve 10 mg of *ergometrine maleate CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *methanol R*, *methylene chloride R* (3:25:75 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In a current of cold air.

Detection Spray with *dimethylaminobenzaldehyde solution R7* and dry in a current of warm air for about 2 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 0.100 g, without heating and protected from light, in 9 mL of *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_5 or BY_5 (*2.2.2, Method II*).

pH (2.2.3)

3.6 to 4.4 for solution S.

Specific optical rotation (2.2.7)

+ 50 to + 56 (dried substance), determined on solution S.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Solvent mixture acetonitrile R, water R (15:85 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in 10 mL of the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with water R. Dilute 1.0 mL of this solution to 10.0 mL with water R.

Reference solution (b) Dissolve the contents of a vial of ergometrine impurity mixture CRS (impurities D, E, F and I) in 1 mL of a mixture of 30 volumes of mobile phase B and 70 volumes of water R.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography with extended pH range R (3.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 2 g/L solution of ammonium carbamate R;

— *mobile phase B*: acetonitrile R, water for chromatography R (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	85	15
5 - 10	85 → 65	15 → 35
10 - 15	65	35
15 - 20	65 → 20	35 → 80
20 - 25	20	80

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 310 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with ergometrine impurity mixture CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities D, E, F and I.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to ergometrine (retention time = about 11.8 min): impurity D = about 1.3; impurity I = about 1.35; impurity E = about 1.43; impurity F = about 1.55.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurities D and I; minimum 1.5 between the peaks due to impurities I and E.

Calculation of percentage contents:

— for each impurity, use the concentration of ergometrine maleate in reference solution (a).

Limits:

— *impurity F*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 2.0 per cent, determined on 0.200 g by drying *in vacuo* at 80 °C for 2 h.

ASSAY

Dissolve 0.150 g in 40 mL of *anhydrous acetic acid R*. Titrate with *0.05 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.05 M perchloric acid* is equivalent to 22.07 mg of $C_{23}H_{27}N_3O_6$.

STORAGE

In an airtight, glass container, protected from light, at a temperature of 2 °C to 8 °C.

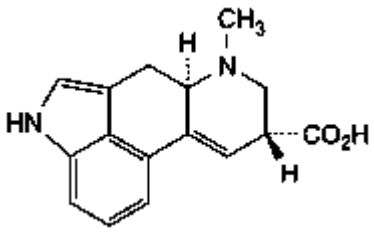
IMPURITIES

Specified impurities *F.*

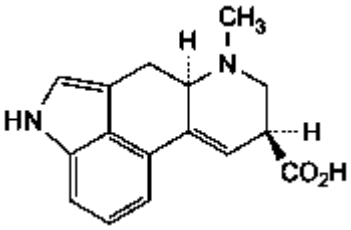
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, G, H, I.*

www.webofpharma.com

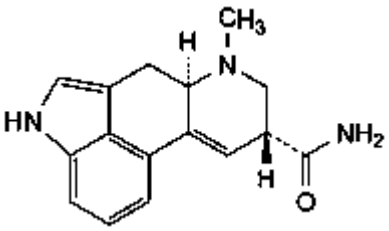
https://thuocngocanh.com/



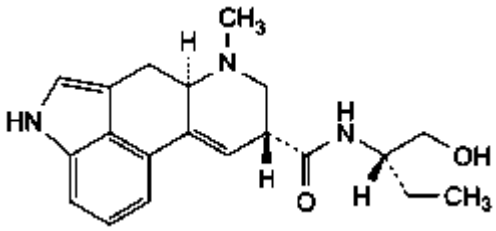
A. (8β)-6-methyl-9,10-didehydroergoline-8-carboxylic acid (lysergic acid),



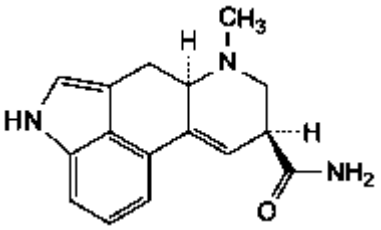
B. (8α)-6-methyl-9,10-didehydroergoline-8-carboxylic acid (isolysergic acid),



C. (8β)-6-methyl-9,10-didehydroergoline-8-carboxamide (ergine),



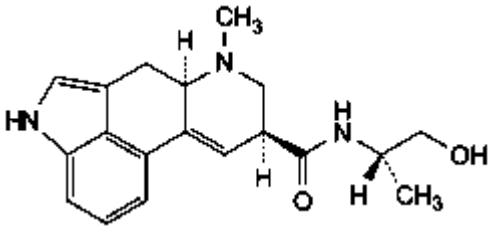
D. (8β)-*N*-[(2*S*)-1-hydroxybutan-2-yl]-6-methyl-9,10-didehydroergoline-8-carboxamide (methylergometrine),



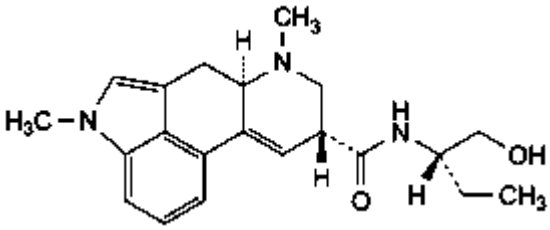
E. (8α)-6-methyl-9,10-didehydroergoline-8-carboxamide (erginine),

www.webofpharma.com

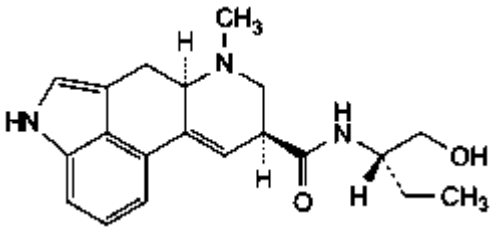
https://thuocngocanh.com/



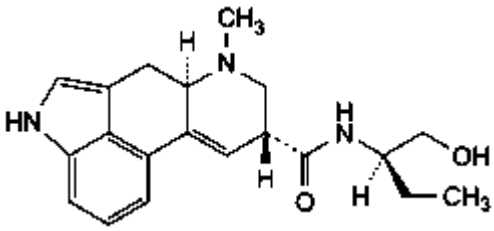
F. (8α)-*N*-[(2*S*)-1-hydroxypropan-2-yl]-6-methyl-9,10-didehydroergoline-8-carboxamide (ergometrinine),



G. (8β)-*N*-[(2*S*)-1-hydroxybutan-2-yl]-1,6-dimethyl-9,10-didehydroergoline-8-carboxamide (methysergide),



H. (8α)-*N*-[(2*S*)-1-hydroxybutan-2-yl]-6-methyl-9,10-didehydroergoline-8-carboxamide (methylergometrinine),



I. (8β)-*N*-[(2*R*)-1-hydroxybutan-2-yl]-6-methyl-9,10-didehydroergoline-8-carboxamide (2′-*epi*-methylergometrine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

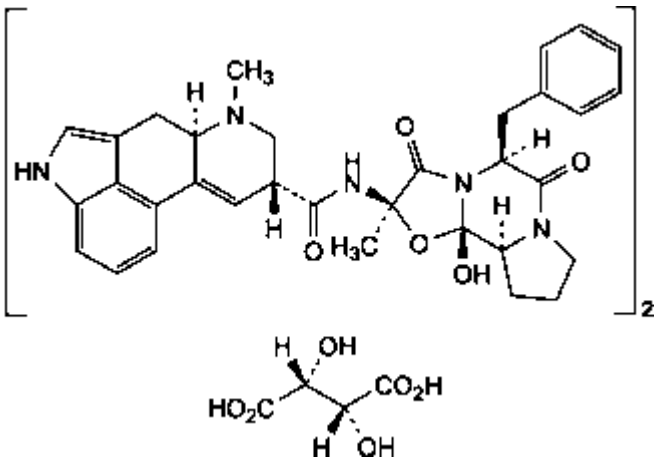
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ergotamine Tartrate

General Notices

(Ph. Eur. monograph 0224)



$C_{70}H_{76}N_{10}O_{16}$ 1313 *379-79-3*

Action and use

Oxytocic.

Ph Eur

DEFINITION

Bis[(6a*R*,9*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide] (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

98.0 per cent to 101.0 per cent (dried substance).

It may contain two molecules of methanol of crystallisation.

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals, slightly hygroscopic.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Slightly soluble in ethanol 96 per cent. Aqueous solutions slowly become cloudy owing to hydrolysis; this may be prevented by the addition of tartaric acid.

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ergotamine tartrate CRS*.

Preparation As discs, triturate the substance to be examined and the reference substance separately with 0.2 mL of *methanol R* and then with *potassium bromide R* as prescribed in the general method.

B. Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use.*

Test solution Dissolve 5 mg of the substance to be examined in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5.0 mL with the same mixture of solvents.

Reference solution Dissolve 5 mg of *ergotamine tartrate CRS* in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 5.0 mL with the same mixture of solvents.

Plate *TLC silica gel plate R*.

Mobile phase *anhydrous ethanol R*, *methylene chloride R*, *dimethylformamide R*, *ether R* (5:10:15:70 *V/V/V/V*).

Application 5 µL; immediately expose the points of application to ammonia vapour for exactly 20 s by moving the line of application from side to side above a beaker 55 mm high and 45 mm in diameter containing about 20 mL of *concentrated ammonia R*; dry the line of application in a current of cold air for exactly 20 s.

Development Over 2/3 of the plate.

Drying In a current of cold air for about 2 min.

Detection A Examine for not more than 1 min in ultraviolet light at 365 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and fluorescence to the principal spot in the chromatogram obtained with the reference solution.

Detection B Spray the plate abundantly with *dimethylaminobenzaldehyde solution R7* and dry in a current of warm air for about 2 min; examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

www.webofpharma.com

https://thuocngocanh.com/

C. To 0.1 mL of solution S (see Tests) add 1 mL of *glacial acetic acid R*, 0.05 mL of *ferric chloride solution R1* and 1 mL of *phosphoric acid R* and heat in a water-bath at 80 °C. After about 10 min, a blue or violet colour develops which becomes more intense on standing.

D. Dissolve about 10 mg in 1.0 mL of *0.1 M sodium hydroxide*. Transfer to a separating funnel and shake with 5 mL of *methylene chloride R*. Discard the organic layer. Neutralise the aqueous layer with a few drops of *dilute hydrochloric acid R*. 0.1 mL of this solution gives reaction (b) of tartrates (*2.3.1*). Pour the reaction mixture into 1 mL of *water R* to observe the colour change to red or brownish-red.

TESTS

Carry out all operations as rapidly as possible, protected from light.

Solution S

Triturate 50 mg finely with about 25 mg of *tartaric acid R* and dissolve with shaking in 10 mL of *water R*.

pH (*2.2.3*)

4.0 to 5.5 for the suspension.

Shake 25 mg, finely powdered, with 10 mL of *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*): use the normalisation procedure. *Prepare the solutions immediately before use.*

Solvent mixture *water R*, *acetonitrile R* (10:90 *V/V*).

Solution A Dissolve 1.0 g of *potassium dihydrogen phosphate R* and 2.0 g of *sodium 1-propanesulfonate R* in 900 mL of *water R*, adjust to pH 4.3 with *dilute phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 30 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution Dissolve 3 mg of *ergotamine for system suitability CRS* (containing impurities A and C) in the solvent mixture and dilute to 5 mL with the solvent mixture. In order to prepare impurity B *in situ*, maintain the solution at room temperature for 1 h.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (1.8 µm);

— *temperature*: 15 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, solution A (10:90 *V/V*);

— *mobile phase B*: solution A, *acetonitrile for chromatography R* (20:80 *V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	80 → 50	20 → 50

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 240 nm.

Autosampler Set at 4 °C.

Injection 1 µL.

Identification of impurities Use the chromatogram supplied with *ergotamine for system suitability CRS* and the chromatogram obtained with the reference solution to identify the peaks due to impurities A, B and C.

Relative retention With reference to ergotamine (retention time = about 3 min): impurity A = about 0.9; impurity B = about 1.1; impurity C = about 1.2.

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to impurity A and ergotamine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.3;

— *impurity C*: maximum 0.4 per cent;

— *impurities A, B*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 6.0 per cent, determined on 0.100 g by drying *in vacuo* at 95 °C for 6 h.

ASSAY

Dissolve 0.200 g in 40 mL of *anhydrous acetic acid R*. Titrate with *0.05 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.05 M perchloric acid* is equivalent to 32.84 mg of $C_{70}H_{76}N_{10}O_{16}$.

STORAGE

www.webofpharma.com

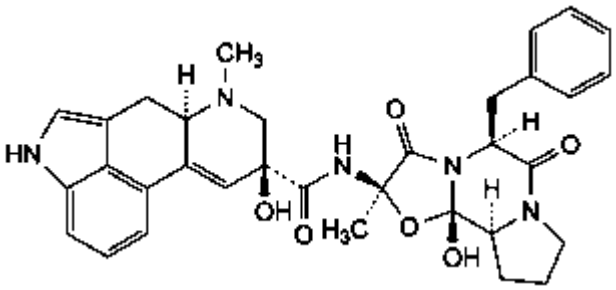
https://thuocngocanh.com/

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

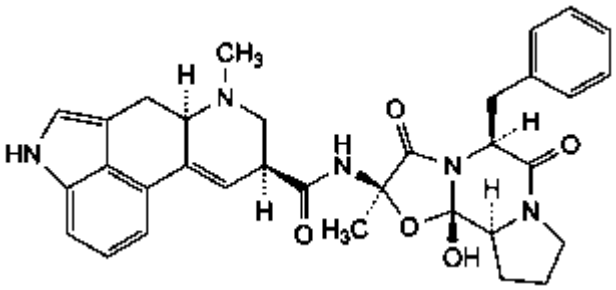
IMPURITIES

Specified impurities *A, B, C.*

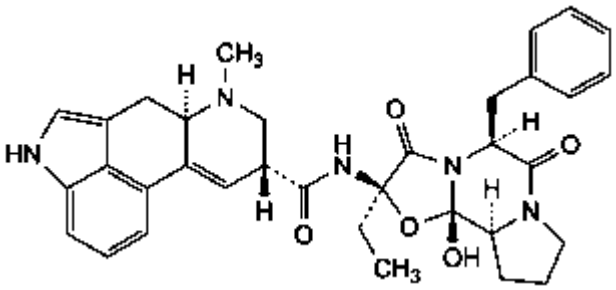
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*



A. (6a*R*,9*S*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-9-hydroxy-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (8-hydroxyergotamine),



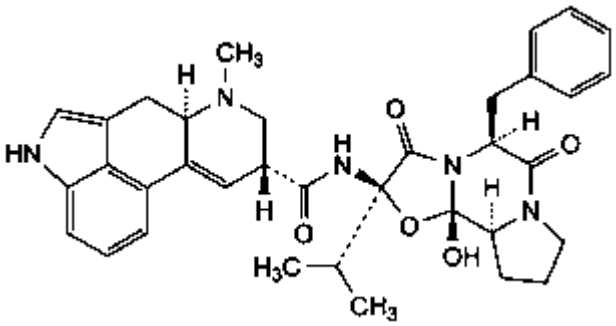
B. (6a*R*,9*S*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (ergotaminine),



C. (6a*R*,9*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-2-ethyl-10b-hydroxy-3,6-dioxooctahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (ergostine),

www.webofpharma.com

https://thuocngocanh.com/



D. (6a*R*,9*R*)-*N*-[(2*R*,5*S*,10a*S*,10b*S*)-5-benzyl-10b-hydroxy-3,6-dioxo-2-(propan-2-yl)octahydro-8*H*-[1,3]oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2-yl]-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide (ergocristine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

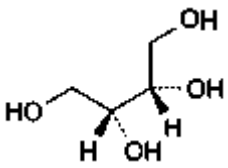
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythritol

General Notices

(Ph. Eur. monograph 1803)



$C_4H_{10}O_4$ 122.1 *149-32-6*

Action and use

Excipient.

Ph Eur

DEFINITION

(2*R*,3*S*)-Butane-1,2,3,4-tetrol (*meso*-erythritol).

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or free-flowing granules.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 119 °C to 122 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *erythritol CRS*.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 5.0 g in *water R* and dilute to 50 mL with the same solvent.

Conductivity (*2.2.38*)

Maximum 20 μS·cm^{-1}.

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution, while gently stirring with a magnetic stirrer.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.50 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.50 g of *erythritol CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 100.0 mL with *water R*.

Reference solution (d) Dissolve 1.0 g of *erythritol R* and 1.0 g of *glycerol R* in *water R* and dilute to 20 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 8.0 mm;

— *stationary phase*: *cation-exchange resin R* (9 μm);

— *temperature*: 70 °C.

Mobile phase 0.01 per cent *V/V* solution of *sulfuric acid R*.

Flow rate 0.8 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Injection 20 μL of the test solution and reference solutions (b), (c) and (d).

Run time 3 times the retention time of erythritol.

Relative retention With reference to erythritol (retention time = about 11 min): impurity A = about 0.77; impurity B = about 0.90; impurity C = about 0.94; impurity D = about 1.10.

System suitability Reference solution (d):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 2.0 between the peaks due to erythritol and impurity D.

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Microbial contamination

If intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

If not intended for use in the manufacture of parenteral preparations:

— TAMC: acceptance criterion 10^3 CFU/g (2.6.12);

— TYMC: acceptance criterion 10^2 CFU/g (2.6.12);

— absence of *Escherichia coli* (2.6.13);

— absence of *Salmonella* (2.6.13).

Bacterial endotoxins (2.6.14)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins:

— less than 4 IU/g for parenteral preparations having a concentration of 100 g/L or less of erythritol;

— less than 2.5 IU/g for parenteral preparations having a concentration of more than 100 g/L of erythritol.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_4H_{10}O_4$ taking into account the assigned content of *erythritol CRS*.

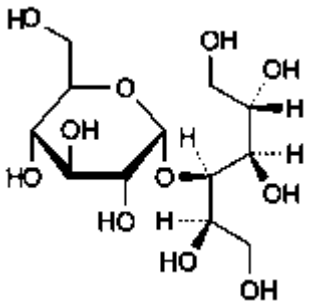
LABELLING

www.webofpharma.com

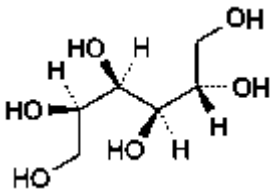
https://thuocngocanh.com/

The label states where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

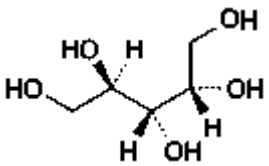
IMPURITIES



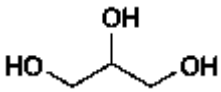
A. 4-*O*-α-D-glucopyranosyl-D-glucitol (D-maltitol),



B. D-glucitol (D-sorbitol),



C. (2*R*,3*s*,4*S*)-pentane-1,2,3,4,5-pentol (*meso*-ribitol),



D. propane-1,2,3-triol (glycerol).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

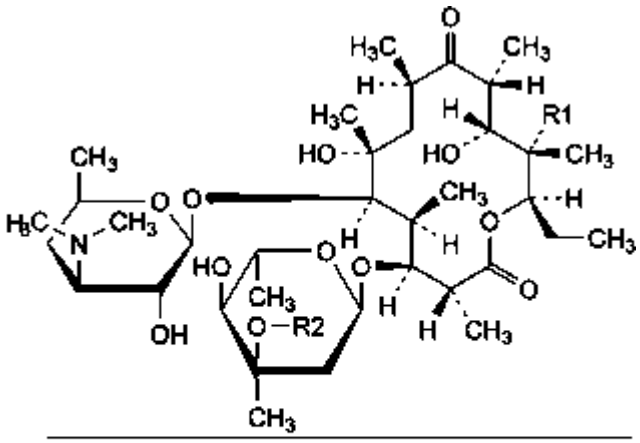
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Erythromycin

General Notices

(Ph. Eur. monograph 0179)



Erythromycin	Mol. Formula	M_r	R1	R2
A	$C_{37}H_{67}NO_{13}$	734	OH	CH_3
B	$C_{37}H_{67}NO_{12}$	718	H	CH_3
C	$C_{36}H_{65}NO_{13}$	720	OH	H

Action and use

Macrolide antibacterial.

Preparations

Erythromycin Gastro-resistant Capsules

Erythromycin Gastro-resistant Tablets

Erythromycin and Zinc Acetate Lotion

Ph Eur

DEFINITION

Mixture of macrolide antibiotics produced by a strain of *Streptomyces erythreus*.

Main component (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxacyclotetradecane-2,10-

www.webofpharma.com

https://thuocngocanh.com/

dione (erythromycin A).

Content

— *sum of erythromycins A, B and C*: 93.0 per cent to 102.0 per cent (anhydrous substance);

— *erythromycin B*: maximum 5.0 per cent (anhydrous substance);

— *erythromycin C*: maximum 5.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow powder or colourless or slightly yellow crystals, slightly hygroscopic.

Solubility

Slightly soluble in water (the solubility decreases as the temperature rises), freely soluble in ethanol (96 per cent), soluble in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *erythromycin A CRS*.

Disregard any band in the region from 1980 cm^{-1} to 2050 cm^{-1}.

If the spectra obtained show differences, dissolve 50 mg of the substance to be examined and of the reference substance separately in 1.0 mL of *methylene chloride R*, dry *in vacuo* at 60 °C for 3 h at a pressure not exceeding 0.7 kPa and record new spectra using the residues.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *erythromycin A CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *spiramycin CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 4 volumes of *2-propanol R*, 8 volumes of a 150 g/L solution of *ammonium acetate R* previously adjusted to pH 9.6 with *ammonia R*, and 9 volumes of *ethyl acetate R*; allow to settle and use the upper layer.

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *anisaldehyde solution R1* and heat at 110 °C for 5 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a), and its position and colour are different from those of the spots in the chromatogram obtained with reference solution (b).

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solution A Dissolve 11.5 g of *dipotassium hydrogen phosphate R* in 900 mL of *water R*, adjust to pH 8.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture *methanol R*, solution A (40:60 *V/V*).

Test solution Dissolve 40.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 40.0 mg of *erythromycin A CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *erythromycin B CRS* and 10.0 mg of *erythromycin C CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 4 mg of *erythromycin for system suitability CRS* (containing impurities A, B, C, D, E, F, H and L) in the solvent mixture and dilute to 1 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (3.5 µm);

— *temperature*: 65 °C; preheating the mobile phase may be required, for instance by extending the inlet tubing in the oven to 30 cm.

Mobile phase:

— *mobile phase A*: *phosphate buffer solution pH 7.0 R7*, *acetonitrile R1*, *water for chromatography R* (5:35:60 *V/V/V*);

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: *phosphate buffer solution pH 7.0 R7*, *water for chromatography R*, *acetonitrile R1* (5:45:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	100	0
t_R - (t_R + 2)	100 → 0	0 → 100
(t_R + 2) - (t_R + 15)	0	100

t_R = retention time of erythromycin B, determined by injecting 10 µL of reference solution (b) and eluting with mobile phase A.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 4 °C.

Injection 100 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *erythromycin for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, E, F, H and L; use the chromatogram obtained with reference solution (b) to identify the peaks due to erythromycins B and C.

Relative retention With reference to erythromycin A (retention time = about 23 min): impurity H = about 0.3; impurity A = about 0.4; impurity B = about 0.5; erythromycin C = about 0.55; impurity L = about 0.63; impurity C = about 0.9; impurity D = about 1.61; erythromycin B = about 1.75; impurity F = about 1.81; impurity E = about 2.3.

System suitability Reference solution (d):

— *resolution*: minimum 1.2 between the peaks due to impurity B and erythromycin C;

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B; minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A. If necessary, adjust the concentration of acetonitrile in the mobile phases and/or the gradient to obtain the required separation.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 2; impurity E = 0.08; impurity F = 0.08; impurity L = 0.11;

— for each impurity, use the concentration of erythromycin A in reference solution (c).

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity C*: maximum 3.0 per cent;

— *impurities A, B*: for each impurity, maximum 2.0 per cent;

— *impurities D, E, F, H*: for each impurity, maximum 1.0 per cent;

— *impurity L*: maximum 0.4 per cent;

— *any other impurity*: for each impurity, maximum 0.4 per cent;

— *total*: maximum 7.0 per cent;

— *reporting threshold*: 0.2 per cent; disregard the peaks due to erythromycins B and C.

Thiocyanate

Maximum 0.3 per cent.

Prepare the solutions immediately before use and protect from actinic light.

Compensation liquid Dilute 1.0 mL of a 90 g/L solution of *ferric chloride R* to 50.0 mL with *methanol R*.

Test solution Dissolve 0.100 g of the substance to be examined in 20 mL of *methanol R*, add 1.0 mL of a 90 g/L solution of *ferric chloride R* and dilute to 50.0 mL with *methanol R*.

Prepare 2 independent reference solutions.

Reference solution Dissolve 0.100 g of *potassium thiocyanate R*, previously dried at 105 °C for 1 h, in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *methanol R*. To 5.0 mL of this solution, add 1.0 mL of a 90 g/L solution of *ferric chloride R* and dilute to 50.0 mL with *methanol R*.

Measure the absorbance (*2.2.25*) of each reference solution (A_1, A_2) and of the test solution (A) at the absorption maximum (about 492 nm).

Suitability value:

$$S = \frac{m_2 \times A_1}{m_1 \times A_2}$$

m_1, m_2 = mass of potassium thiocyanate used to prepare reference solutions A_1 and A_2 respectively, in grams.

The test is not valid unless S is not less than 0.985 and not greater than 1.015.

Calculate the percentage content of thiocyanate using the following expression:

$$\frac{A \times 58.08 \times 0.5}{m \times 97.18} \times \left(\frac{m_1}{A_1} + \frac{m_2}{A_2} \right)$$

m = mass of the substance to be examined used to prepare the test solution, in grams;

www.webofpharma.com

https://thuocngocanh.com/

58.08	=	relative molecular mass of the thiocyanate moiety;
97.18	=	relative molecular mass of potassium thiocyanate.

Water (*2.5.12*)

Maximum 6.5 per cent, determined on 0.200 g.

Use a 100 g/L solution of *imidazole R* in *anhydrous methanol R* as the solvent.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solutions (a) and (b).

System suitability Reference solution (a):

— *symmetry factor*: maximum 2.5 for the peak due to erythromycin A;

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$) using the chromatogram obtained with reference solution (a). Calculate the percentage contents of erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatogram obtained with reference solution (b).

STORAGE

In an airtight container, protected from light.

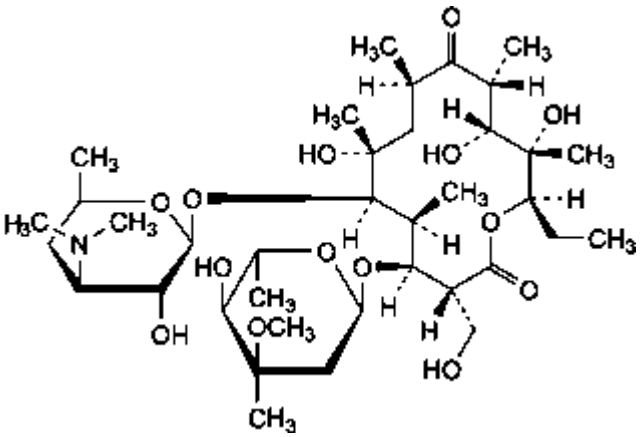
IMPURITIES

Specified impurities *A, B, C, D, E, F, H, L.*

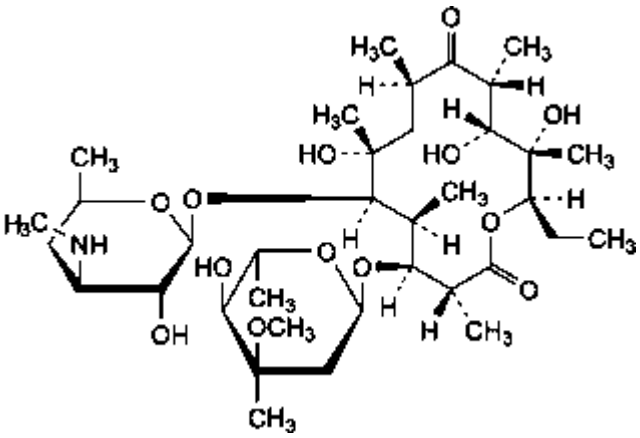
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *I, J, K, M, N.*

www.webofpharma.com

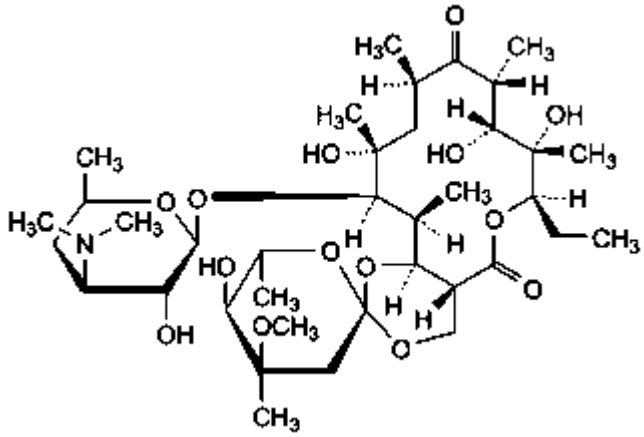
https://thuocngocanh.com/



A. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxacyclotetradecane-2,10-dione (erythromycin F),



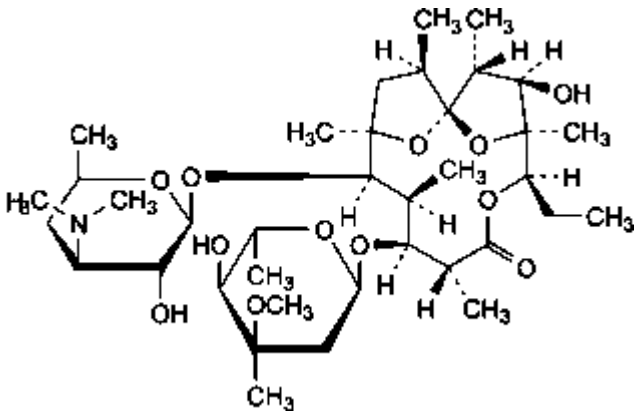
B. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(methylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxacyclotetradecane-2,10-dione (3″-*N*-demethylerythromycin A),



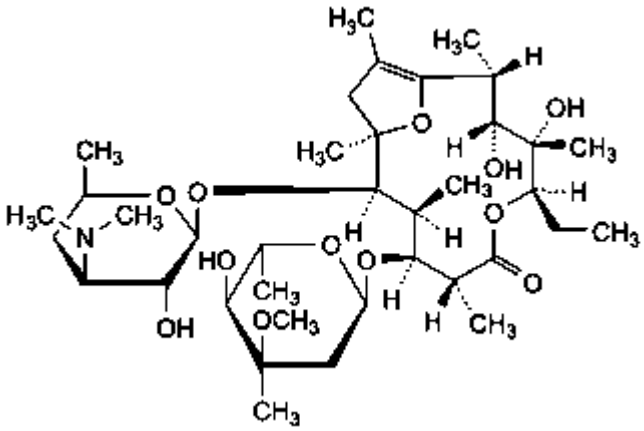
C. (2*S*,4a*R*,4′*R*,5′*S*,6′*S*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,15*R*,16*S*,16a*S*)-7-ethyl-5′,8,9,14-tetrahydroxy-4′-methoxy-4′,6′,8,10,12,14,16-heptamethyl-15-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,4a,7,8,9,10,12,13,14,15,16,16a-dodecahydro-5*H*,11*H*-spiro[[1,3]dioxino[5,4-*c*][1]oxacyclotetradecin-2,2′-oxane]-5,11-dione (erythromycin E),

www.webofpharma.com

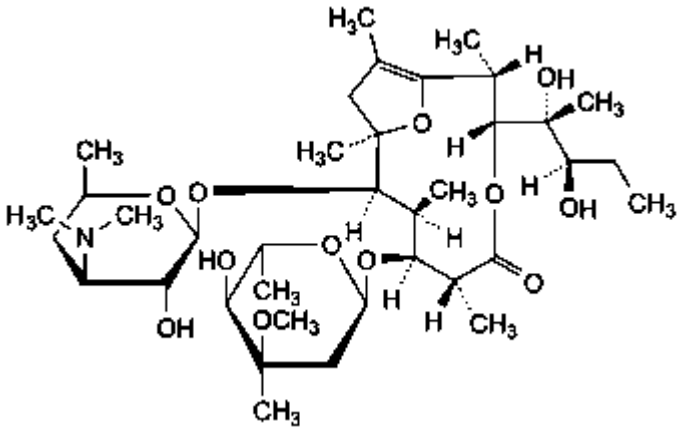
https://thuocngocanh.com/



D. (1*S*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadecan-7-one (anhydroerythromycin A),



E. (1^{5}*R*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-1^{3},1^{5},2,4,8,10-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1^{4},1^{5}-dihydro-6-oxa-1(2,5)-furanacycloundecaphan-7-one (erythromycin A enol ether),

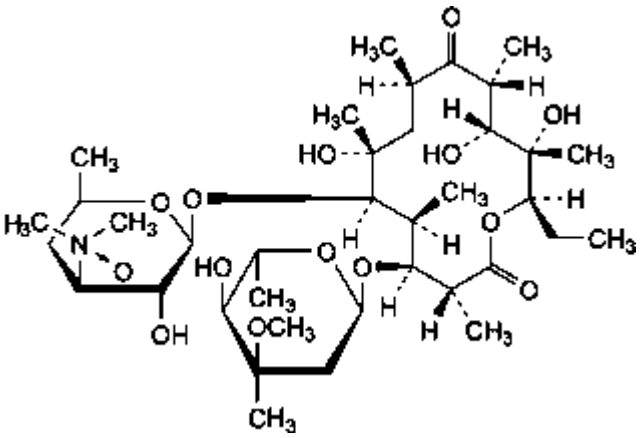


F. (1^{5}*R*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(2*R*,3*R*)-2,3-dihydroxypentan-2-yl]-1^{3},1^{5},2,6,8-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1^{4},1^{5}-dihydro-4-oxa-1(2,5)-

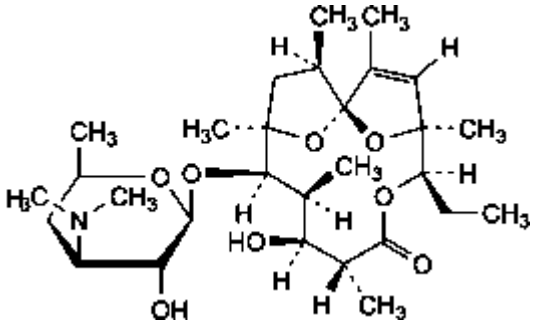
www.webofpharma.com

https://thuocngocanh.com/

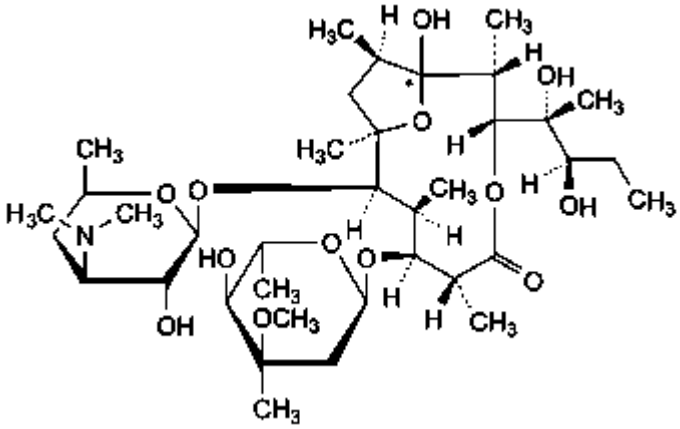
furanacyclononaphan-5-one (pseudoerythromycin A enol ether),



H. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-2,10-dioxo-1-oxacyclotetradecan-6-yl 3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranoside *N*-oxide (erythromycin A 3″-*N*-oxide),



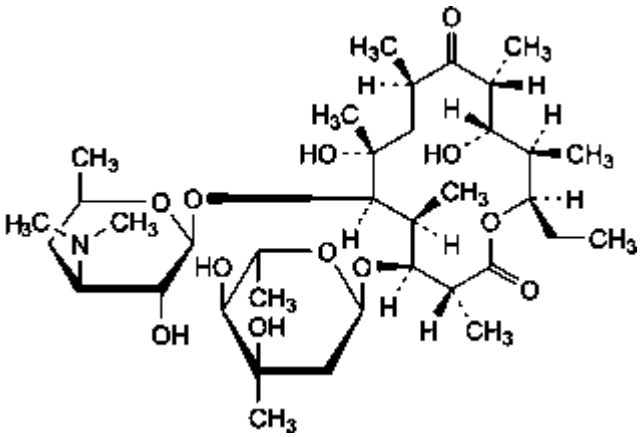
I. (1*S*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-5-ethyl-9-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadec-2-en-7-one (erythralosamine),



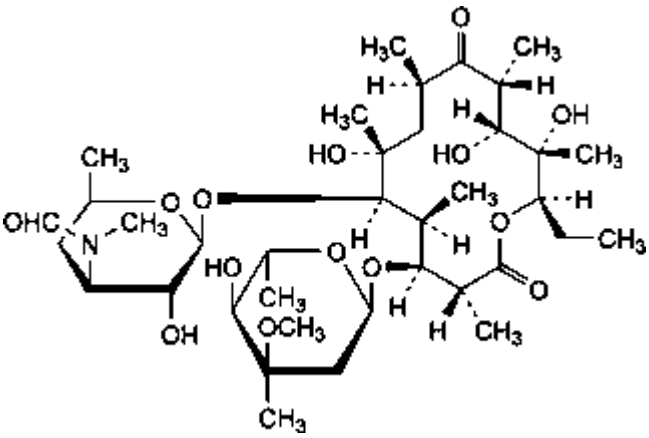
J. (1*RS*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*)-7-[(2,6-dideoxy-3-[(2*R*,3*R*)-2,3-dihydroxypentan-2-yl]-1-hydroxy-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridecan-5-one (pseudoerythromycin A hemiketal),

www.webofpharma.com

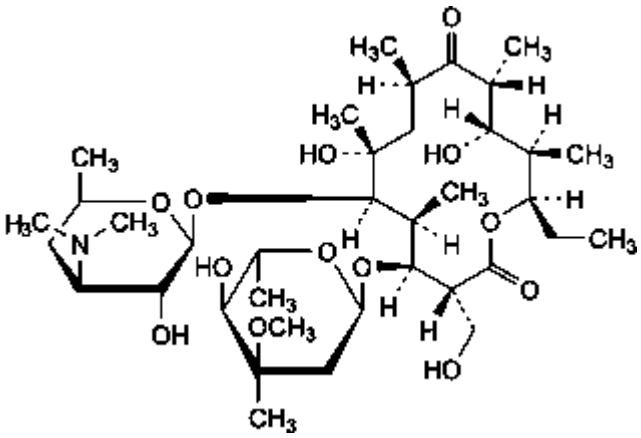
https://thuocngocanh.com/



K. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxacyclotetradecane-2,10-dione (erythromycin D),



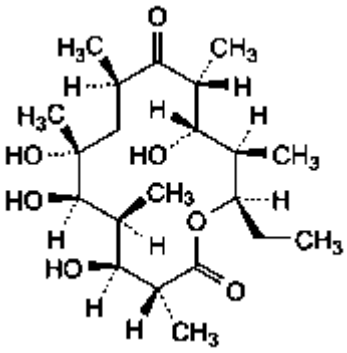
L. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-[formyl(methyl)amino]-β-D-*xylo*-hexopyranosyl]oxy]-1-oxacyclotetradecane-2,10-dione (3″-*N*-demethyl-3″-*N*-formyl erythromycin A),



M. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxacyclotetradecane-2,10-dione (erythromycin G),

www.webofpharma.com

https://thuocngocanh.com/



N. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-14-ethyl-4,6,7,12-tetrahydroxy-3,5,7,9,11,13-hexamethyl-1-oxacyclotetradecane-2,10-dione (erythronolide B).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin and Zinc Acetate Lotion

General Notices

Erythromycin and Zinc Acetate Cutaneous Solution

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin and Zinc Acetate Lotion is a *cutaneous solution*. It contains 4% w/v of Erythromycin and 1.2% w/v of Zinc Acetate in a suitable ethanolic vehicle. It is prepared by dissolving the dry ingredients in the requisite volume of the vehicle provided before use.

The lotion complies with the requirements stated under Liquids for Cutaneous Application.

The dry ingredients comply with the requirements for Powders for Lotions stated under Liquids for Cutaneous Application and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)

95.0 to 110.0% of the stated amount of Erythromycin.

Content of zinc acetate, $C_4H_6O_4Zn,2H_2O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay for erythromycin, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Mix a quantity of the powder with sufficient *water* to produce a 5% w/v solution and filter. Add 0.5 mL of a 0.25M solution of *potassium hexacyanoferrate(II)* to 5 mL of the resulting solution and mix; a white precipitate is produced. Add 5 mL of 4M *hydrochloric acid*; the precipitate does not dissolve.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A. *Prepare the solutions immediately before use and protect from light.*

www.webofpharma.com

https://thuocngocanh.com/

Solution A 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol R1*.

(1) Dissolve a quantity of the powder in solution A and dilute to produce a solution containing 0.4% w/v of erythromycin.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

(4) 0.4% w/v of *erythromycin for impurity M identification EPCRS*.

(5) Dilute 1 volumes of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (X-Terra RP18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 65°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 35 volumes of *acetonitrile R1* and 60 volumes of *water*.

Mobile phase B 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 50 volumes of *acetonitrile R1* and 45 volumes of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-44	100	0	isocratic
44-46	100→0	0→100	linear gradient
46-61	0	100	isocratic
61-63	0→100	100→0	linear gradient
63-80	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to erythromycin A (retention time about 23 minutes) are: impurity H, about 0.3; impurity A, about 0.4; impurity B, about 0.5; erythromycin C, about 0.55; impurity M, about 0.58; impurity L, about 0.63; impurity C, about 0.9; impurity D, about 1.6; erythromycin B, about 1.75; impurity F, about 1.8 and impurity E, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

www.webofpharma.com

https://thuocngocanh.com/

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

LIMITS

Identify any peaks corresponding to impurities D, E, F and L in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the corresponding correction factors: impurity D, 2.0; impurity E, 0.08; impurity F, 0.08; impurity L, 0.11.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity A or B is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (2% of each);

the area of any peak corresponding to impurity D, E, F, H or M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak corresponding to impurity L is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak*, other than the peaks due to erythromycin B and C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any *secondary peaks*, other than the peaks due to erythromycin B and C is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peak due to erythromycin B and erythromycin C and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%).

The content of each of erythromycin B and erythromycin C, as determined under Assay, is not more than 5%.

ASSAY

For erythromycin

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A. *Prepare the solutions immediately before use and protect from light.*

Solution A 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Dissolve a quantity of the powder containing 0.4 g of erythromycin in 75 mL of solution A and shake. Dilute to 100 mL.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.4% w/v of *erythromycin BPCRS*.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

DETERMINATION OF CONTENT

Calculate the percentage content of erythromycin A($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatograms obtained with solutions (1) and (2) and the declared contents of $C_{37}H_{67}NO_{13}$, $C_{37}H_{67}NO_{12}$ and $C_{36}H_{65}NO_{13}$ respectively in *erythromycin BPCRS*.

For zinc acetate

To a quantity of the powder containing 0.2 g of Zinc Acetate add 5 mL of *dilute acetic acid*. Carry out the *complexometric titration of zinc*, Appendix VIII D. Each mL of *0.1M disodium edetate VS* is equivalent to 21.95 mg of $C_4H_6O_4Zn,2H_2O$.

For the following tests prepare the lotion as directed on the label. The lotion complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)

90.0 to 110.0% of the stated amount of Erythromycin.

Content of zinc acetate, $C_4H_6O_4Zn,2H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. In the Assay for erythromycin, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Evaporate a suitable volume of the lotion to dryness on a water bath, add 20 mL of water to the residue, mix, with shaking, and filter. Add 1 mL of a 0.25M solution of *potassium hexacyanoferrate(II)* to the resulting filtrate and mix; a white precipitate is produced. Add 10 mL

www.webofpharma.com

https://thuocngocanh.com/

of 4M *hydrochloric acid*; the precipitate does not dissolve.

TESTS

Clarity and colour of solution

The solution is *clear*, Appendix IV A, and *colourless*, Appendix IV B, Method I.

ASSAY

For erythromycin

Carry out the Assay for erythromycin described in the requirements for the dry ingredients. For solution (1) use a volume of the lotion containing 80 mg of Erythromycin in place of the powder.

For zinc acetate

To a volume of the lotion containing 0.2 g of Zinc Acetate add 5 mL of *dilute acetic acid*. Carry out the *complexometric titration of zinc*, Appendix VIII D. Each mL of 0.1M *disodium edetate VS* is equivalent to 21.95 mg of $C_4H_6O_4Zn,2H_2O$.

STORAGE

Erythromycin and Zinc Acetate Lotion should be stored at the temperature and used within the period stated on the label.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Erythromycin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

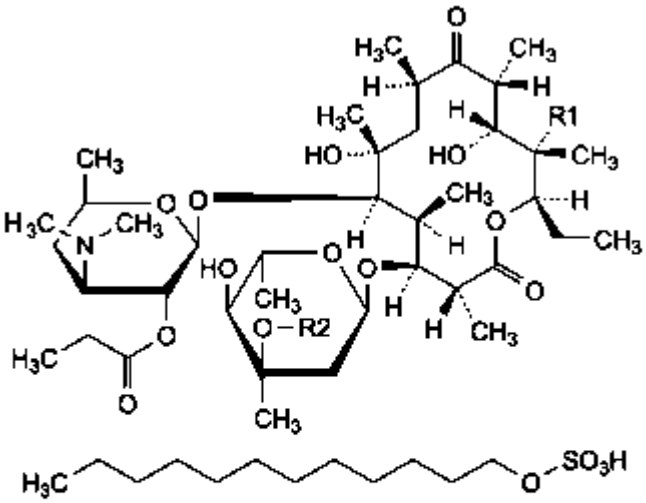
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Erythromycin Estolate

General Notices

(Ph. Eur. monograph 0552)



Erythromycin (estolate)	Mol. Formula	M_r	R1	R2
A	$C_{52}H_{97}NO_{18}S$	1056	OH	CH_3
B	$C_{52}H_{97}NO_{17}S$	1040	H	CH_3
C	$C_{51}H_{95}NO_{18}S$	1042	OH	H

Action and use

Macrolide antibacterial.

Preparation

Erythromycin Estolate Capsules

Ph Eur

DEFINITION

Mixture of the estolate esters of erythromycin.

Main component (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-2-*O*-propanyl-β-D-*xylo*-

www.webofpharma.com

https://thuocngocanh.com/

hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione dodecyl sulfate (erythromycin A 2″-propionate dodecyl sulfate).

Semi-synthetic product derived from a fermentation product obtained using a strain of *Streptomycines erythreus*.

Content

— *sum of erythromycins A, B and C expressed as estolates*: 93.0 per cent to 102.0 per cent (anhydrous substance);

— *erythromycin B estolate*: maximum 5.0 per cent (anhydrous substance);

— *erythromycin C estolate*: maximum 5.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in acetone. It is practically insoluble in dilute hydrochloric acid.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *erythromycin estolate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use (apart from the test solution).*

Solution A (hydrolysis solution). Dissolve 11.5 g of *dipotassium hydrogen phosphate R* in 900 mL of *water R*, adjust to pH 8.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Test solution Dissolve 0.150 g of the substance to be examined in 25 mL of *methanol R*. Add 20 mL of solution A, mix and allow to stand at room temperature for at least 12 h. Dilute to 50.0 mL with solution A.

Reference solution (a) Dissolve 40.0 mg of *erythromycin A CRS* in 12.0 mL of *methanol R* and dilute to 20.0 mL with solution A.

Reference solution (b) Dissolve 10.0 mg of *erythromycin B CRS* and 10.0 mg of *erythromycin C CRS* in 40.0 mL of *methanol R* and dilute to 100.0 mL with solution A.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with a mixture of 4 volumes of solution A and 6 volumes of *methanol R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dissolve 4 mg of *erythromycin for system suitability CRS* (containing impurities A, B, C, D, E, F, H and L) in 0.4 mL of *methanol R* and add 0.6 mL of solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (3.5 µm);

— *temperature*: 65 °C; preheating the mobile phase may be required, for instance by extending the inlet tubing in the oven to 30 cm.

Mobile phase:

— *mobile phase A*: *phosphate buffer solution pH 7.0 R7*, *acetonitrile R1*, *water for chromatography R* (5:35:60 *V/V/V*);

— *mobile phase B*: *phosphate buffer solution ph 7.0 R7*, *water for chromatography R*, *acetonitrile R1* (5:45:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	100	0
t_R - (t_R + 2)	100 → 0	0 → 100
(t_R + 2) - (t_R + 15)	0	100

t_R = retention time of erythromycin B, determined by injecting 20 µL of reference solution (b) and eluting with mobile phase A

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 4 °C.

Injection 200 µL.

Identification of impurities Use the chromatogram supplied with *erythromycin for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, E, F and L; use the chromatogram obtained with reference solution (b) to identify the peaks due to erythromycins B and C.

Relative retention With reference to erythromycin A (retention time = about 23 min): impurity A = about 0.4; impurity B = about 0.5; erythromycin C = about 0.55; impurity L = about 0.63; impurity C = about 0.9; impurity D = about 1.61; erythromycin B = about 1.75; impurity F = about 1.81; impurity E = about 2.3.

System suitability Reference solution (d):

— *resolution*: minimum 1.2 between the peaks due to impurity B and erythromycin C;

www.webofpharma.com

https://thuocngocanh.com/

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B; minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A. If necessary, adjust the concentration of *acetonitrile R1* in the mobile phases and/or the gradient to obtain the required separation.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 2; impurity E = 0.08; impurity F = 0.08; impurity L = 0.11;

— for each impurity, use the concentration of erythromycin A in reference solution (c).

Limits:

— *impurity C*: maximum 3.0 per cent;

— *impurities A, B*: for each impurity, maximum 2.0 per cent;

— *impurities D, F*: for each impurity, maximum 1.0 per cent;

— *impurities eluting with relative retention between 2.1 and 2.4*: not more than 4 impurities; for 1 impurity, maximum 3.5 per cent; for each other impurity, maximum 1.0 per cent;

— *impurity L*: maximum 0.4 per cent;

— *any other impurity*: for each impurity, maximum 0.4 per cent;

— *total*: maximum 7.0 per cent;

— *reporting threshold*: 0.2 per cent; disregard the peaks due to erythromycins B and C and any peak with a relative retention to erythromycin A of less than 0.3 (hydrolysis peaks).

Free erythromycin

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.250 g of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution Dissolve 75.0 mg of *erythromycin A CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 25.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 30 °C.

Mobile phase Mix 35 volumes of *acetonitrile R1* and 65 volumes of a solution containing 3.4 g/L of *potassium dihydrogen phosphate R* and 2.0 g/L of *triethylamine R*, previously adjusted to pH 3.0 with *dilute phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 195 nm.

Injection 20 µL.

Run time Twice the retention time of erythromycin A for the reference solution and 4.5 times the retention time of the 1st peak of erythromycin propionate for the test solution.

Retention time Erythromycin A = about 5 min; 1st peak of erythromycin propionate = about 10 min.

Limit:

— *free erythromycin*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (6.0 per cent).

Dodecyl sulfate

23.0 per cent to 25.5 per cent of $C_{12}H_{26}O_4S$ (anhydrous substance).

Dissolve 0.500 g in 25 mL of *dimethylformamide R*. Titrate with *0.1 M sodium methoxide* using 0.05 mL of a 3 g/L solution of *thymol blue R* in *methanol R* as indicator.

1 mL of *0.1 M sodium methoxide* is equivalent to 26.64 mg of $C_{12}H_{26}O_4S$.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.300 g.

Use a 100 g/L solution of *imidazole R* in *anhydrous methanol R* as the solvent.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 0.5 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solutions (a) and (b).

System suitability Reference solution (a):

— *symmetry factor*: maximum 2.5 for the peak due to erythromycin A;

www.webofpharma.com

https://thuocngocanh.com/

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$) using the chromatogram obtained with reference solution (a). Calculate the percentage contents of erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatogram obtained with reference solution (b). Express the result as erythromycin A estolate, erythromycin B estolate and erythromycin C estolate by multiplying the percentage content of erythromycin A by 1.4387, the percentage content of erythromycin B by 1.4485 and the percentage content of erythromycin C by 1.4472.

For the calculation of content of erythromycin estolate, use the sum of erythromycins A, B and C expressed as estolates as described above.

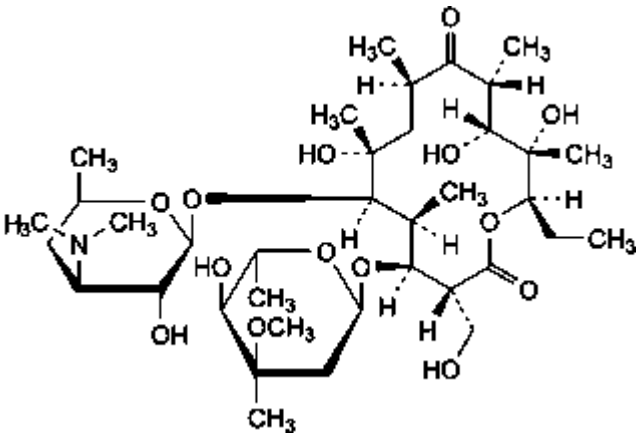
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C, D, E, F, L.*

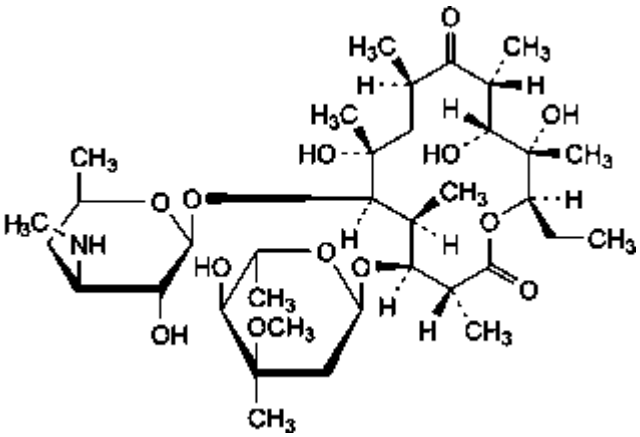
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G, H, I, J, K, M, N.*



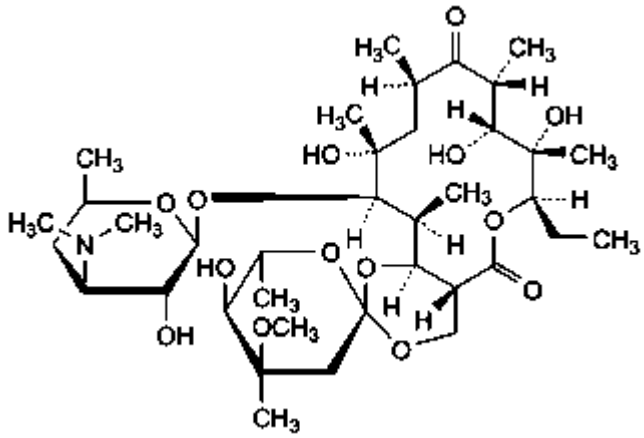
A. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin F),

www.webofpharma.com

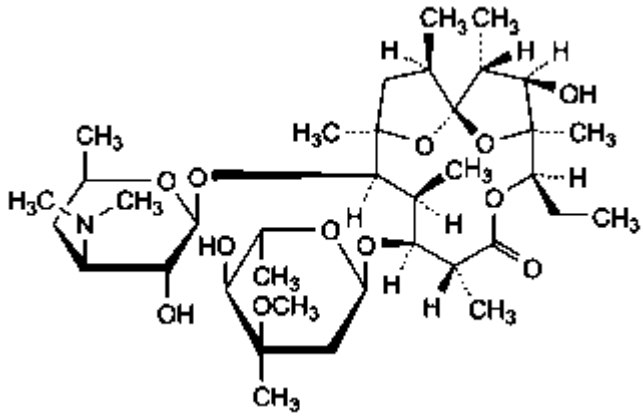
https://thuocngocanh.com/



B. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(methylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethylerythromycin A),



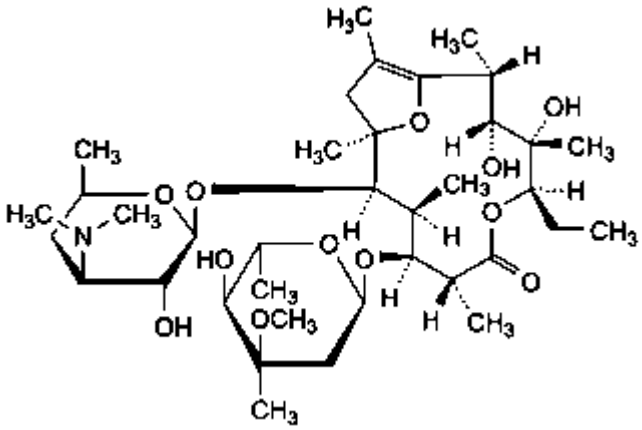
C. (2*S*,4a*R*,4′*R*,5′*S*,6′*S*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,15*R*,16*S*,16a*S*)-7-ethyl-5′,8,9,14-tetrahydroxy-4′-methoxy-4′,6′,8,10,12,14,16-heptamethyl-15-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]hexadecahydrospiro[5*H*,11*H*-1,3-dioxino[5,4-*c*]oxacyclotetradecin-2,2′-pyrane]-5,11-dione (erythromycin E),



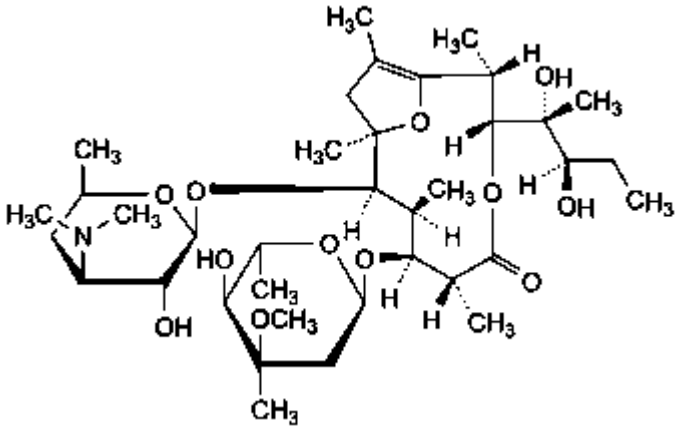
D. (1*S*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadecan-7-one (anhydroerythromycin A),

www.webofpharma.com

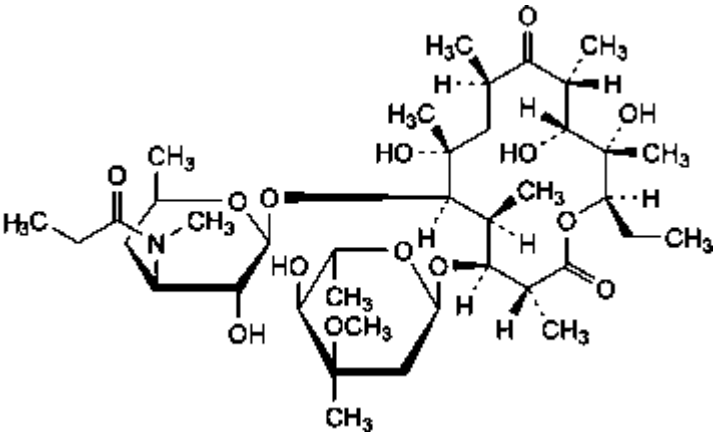
https://thuvienthuocngocanh.com/



E. (2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-en-7-one (erythromycin A enol ether),



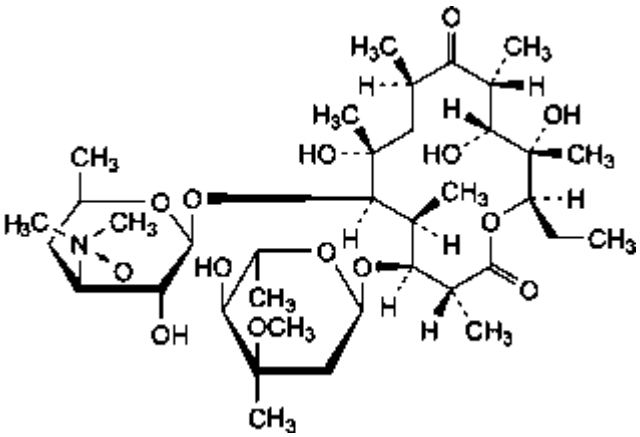
F. (2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one (pseudoerythromycin A enol ether),



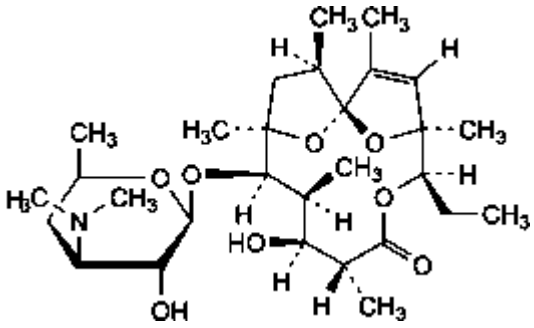
G. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(methylpropanoylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethyl-3″-*N*-propanoylerythromycin A),

www.webofpharma.com

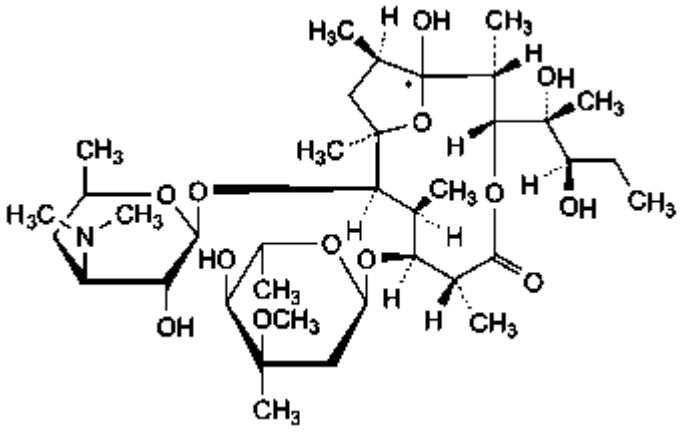
https://thuvienthuocngocanh.com/



H. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione *N*-oxide (erythromycin A 3″-*N*-oxide),



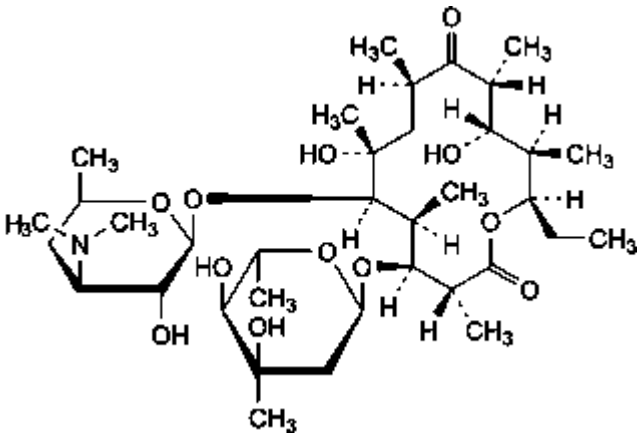
I. (1*S*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-5-ethyl-9-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadec-2-en-7-one (erythralosamine),



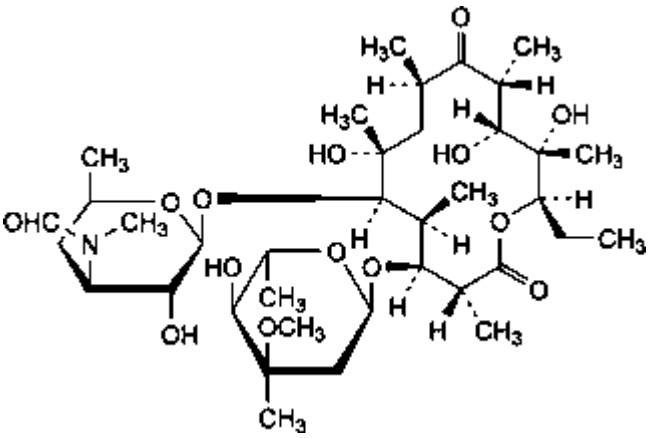
J. (1*RS*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-1-hydroxy-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridecan-5-one (pseudoerythromycin A hemiketal),

www.webofpharma.com

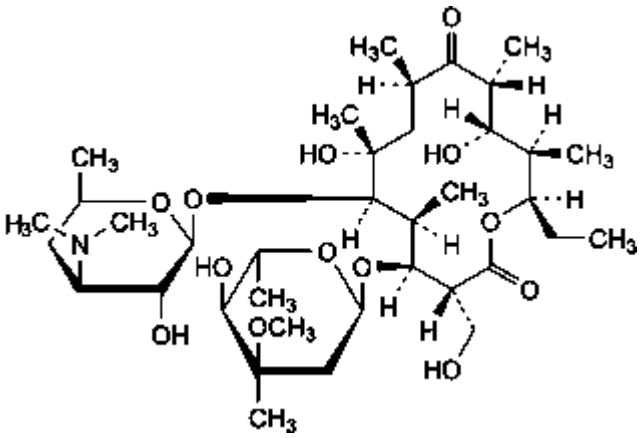
https://thuocngocanh.com/



K. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin D),



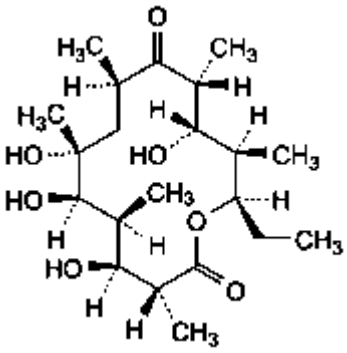
L. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(formylmethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethyl-3″-*N*-formylerythromycin A),



M. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin G),

www.webofpharma.com

https://thuocngocanh.com/



N. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-14-ethyl-4,6,7,12-tetrahydroxy-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione (erythronolide B).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

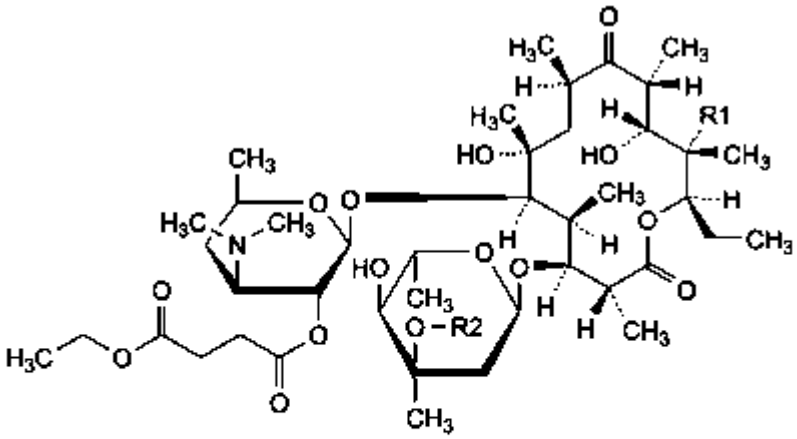
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Erythromycin Ethyl Succinate

General Notices

(Erythromycin Ethylsuccinate, Ph. Eur. monograph 0274)



Erythromycin (ethylsuccinate)	Mol. Formula	M_r	R1	R2
A	$C_{43}H_{75}NO_{16}$	862	OH	CH_3
B	$C_{43}H_{75}NO_{15}$	846	H	CH_3
C	$C_{42}H_{73}NO_{16}$	848	OH	H

Action and use

Macrolide antibacterial.

Preparations

Erythromycin Ethyl Succinate Oral Suspension

Erythromycin Ethyl Succinate Tablets

Ph Eur

DEFINITION

Mixture of the ethylsuccinate esters of erythromycin.

Main component (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-2-*O*-(4-ethoxy-4-oxobutanoyl)-β-D-*xylo*-

www.webofpharma.com

https://thuocngocanh.com/

hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin A 2″-(ethyl succinate)).

Semi-synthetic product derived from a fermentation product obtained using a strain of *Streptomyces erythreus*.

Content

— *sum of erythromycins A, B and C expressed as ethylsuccinates*: 93.0 per cent to 102.0 per cent (anhydrous substance);

— *erythromycin B ethylsuccinate*: maximum 5.0 per cent (anhydrous substance);

— *erythromycin C ethylsuccinate*: maximum 5.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Practically insoluble in water, freely soluble in acetone, in anhydrous ethanol and in methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *erythromycin ethylsuccinate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Hydrolysis solution A 20 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 8.0 with *phosphoric acid R*.

Test solution Dissolve 0.115 g of the substance to be examined in 25 mL of *methanol R*. Add 20 mL of the hydrolysis solution, mix and allow to stand at room temperature for at least 12 h. Dilute to 50.0 mL with the hydrolysis solution.

Reference solution (a) Dissolve 40.0 mg of *erythromycin A CRS* in 10 mL of *methanol R* and dilute to 20.0 mL with the hydrolysis solution.

Reference solution (b) Dissolve 10.0 mg of *erythromycin B CRS* and 10.0 mg of *erythromycin C CRS* in 50 mL of *methanol R*. Add 5.0 mL of reference solution (a) and dilute to 100.0 mL with the hydrolysis solution.

Reference solution (c) Dissolve 2 mg of *N-demethylerythromycin A CRS* in 20 mL of reference solution (b).

Reference solution (d) Dilute 3.0 mL of reference solution (a) to 100.0 mL with a mixture of equal volumes of *methanol R* and the hydrolysis solution.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (e) Dissolve 40 mg of *erythromycin A CRS*, previously heated at 130 °C for 3 h, in 10 mL of *methanol R* and dilute to 20 mL with the hydrolysis solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (8 µm) with a pore size of 100 nm;

— *temperature*: 70 °C using a water-bath for the column and at least one-third of the tubing preceding the column.

Mobile phase To 50 mL of a 35 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 8.0 with *dilute phosphoric acid R*, add 400 mL of *water for chromatography R*, 165 mL of *2-methyl-2-propanol R* and 30 mL of *acetonitrile R1*, and dilute to 1000 mL with *water for chromatography R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 200 µL of the test solution and reference solutions (a), (c), (d) and (e).

Run time 5 times the retention time of erythromycin A; begin integration after the hydrolysis peak.

Relative retention With reference to erythromycin A (retention time = about 15 min): hydrolysis peak = less than 0.3; impurity B = about 0.45; erythromycin C = about 0.5; impurity C = about 0.9; impurity G = about 1.3; impurity D = about 1.4; impurity F = about 1.5; erythromycin B = about 1.8; impurity E = about 4.3.

System suitability Reference solution (c):

— *resolution*: minimum 0.8 between the peaks due to impurity B and erythromycin C and minimum 5.5 between the peaks due to impurity B and erythromycin A.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.09; impurity F = 0.15; impurity G = 0.14; use the chromatogram obtained with reference solution (e) to identify the peaks due to impurities E and F;

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (3.0 per cent);

— *total*: not more than 1.67 times the area of the principal peak in the chromatogram obtained with reference solution (d) (5.0 per cent);

— *disregard limit*: 0.02 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.06 per cent).

Free erythromycin

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.250 g of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution Dissolve 75.0 mg of *erythromycin A CRS* in *acetonitrile R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 25.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 35 volumes of *acetonitrile R1* and 65 volumes of a solution containing 3.4 g/L of *potassium dihydrogen phosphate R* and 2.0 g/L of *triethylamine R*, previously adjusted to pH 3.0 with *dilute phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 195 nm.

Injection 20 µL.

Run time Twice the retention time of erythromycin A (retention time = about 8 min) for the reference solution; twice the retention time of erythromycin ethylsuccinate (retention time = about 24 min) for the test solution.

Limit:

— *free erythromycin*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (6.0 per cent).

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.300 g.

Use a 100 g/L solution of *imidazole R* in *anhydrous methanol R* as the solvent.

Sulfated ash (*2.4.14*)

Maximum 0.3 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use (apart from the test solution).*

Solution A (hydrolysis solution). Dissolve 11.5 g of *dipotassium hydrogen phosphate R* in 900 mL of *water R*, adjust to pH 8.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture *methanol R*, solution A (40:60 *V/V*).

Test solution Dissolve 11.5 mg of the substance to be examined in 2.5 mL of *methanol R*. Add 2 mL of solution A, mix and allow to stand at room temperature for at least 12 h. Dilute to 5.0 mL with solution A.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 40.0 mg of *erythromycin A CRS* in 10.0 mL of *methanol R* and dilute to 20.0 mL with solution A.

Reference solution (b) Dissolve 10.0 mg of *erythromycin B CRS* and 10.0 mg of *erythromycin C CRS* in 50.0 mL of *methanol R* and dilute to 100.0 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (3.5 µm);

— *temperature*: 65 °C; preheating the mobile phase may be required, for instance by extending the inlet tubing in the oven to 30 cm.

Mobile phase:

— *mobile phase A*: *phosphate buffer solution pH 7.0 R7*, *acetonitrile R1*, *water for chromatography R* (5:35:60 *V/V/V*);

— *mobile phase B*: *phosphate buffer solution pH 7.0 R7*, *water for chromatography R*, *acetonitrile R1* (5:45:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	100	0
t_R - (t_R + 2)	100 → 0	0 → 100
(t_R + 2) - (t_R + 15)	0	100

t_R = retention time of erythromycin B, determined by injecting 20 µL of reference solution (b) and eluting with mobile phase A

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 4 °C.

Injection 200 µL.

System suitability Reference solution (a):

— *symmetry factor*: maximum 2.5 for the peak due to erythromycin A;

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$) using the chromatogram obtained with reference solution (a). Calculate the percentage contents of erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatogram obtained with reference solution (b).

www.webofpharma.com

https://thuocngocanh.com/

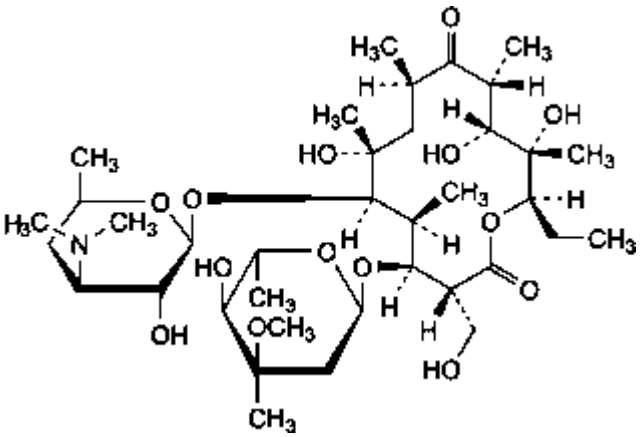
Express the results as erythromycin A ethylsuccinate, erythromycin B ethylsuccinate and erythromycin C ethylsuccinate by multiplying the percentage content of erythromycin A by 1.1744, the percentage content of erythromycin B by 1.1783 and the percentage content of erythromycin C by 1.1777.

For the calculation of content of erythromycin ethylsuccinate, use the sum of erythromycins A, B and C expressed as ethylsuccinates as described above.

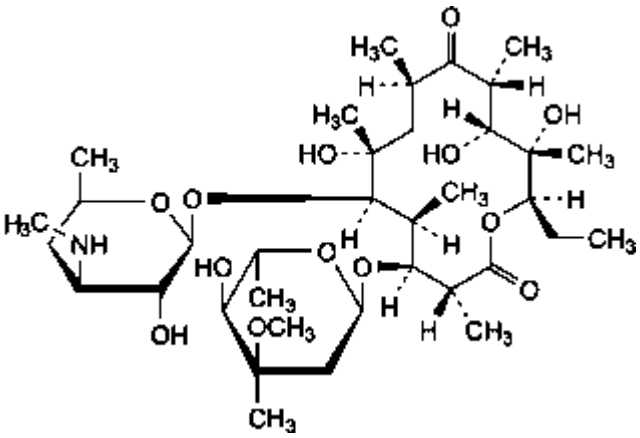
STORAGE

In an airtight container, protected from light.

IMPURITIES



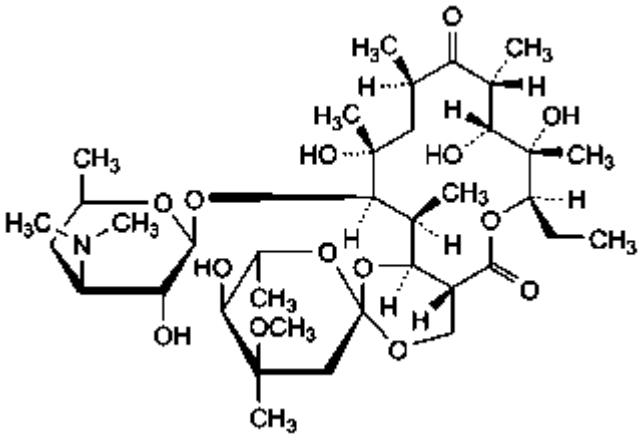
A. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin F),



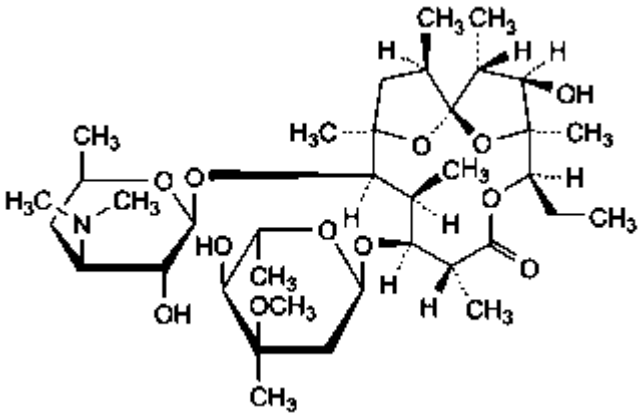
B. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(methylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethylerythromycin A),

www.webofpharma.com

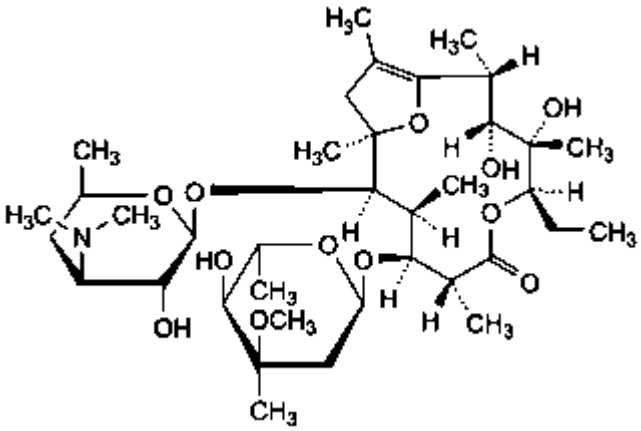
https://thuocngocanh.com/



C. (2*S*,4a*R*,4′*R*,5′*S*,6′*S*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,15*R*,16*S*,16a*S*)-7-ethyl-5′,8,9,14-tetrahydroxy-4′-methoxy-4′,6′,8,10,12,14,16-heptamethyl-15-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]hexadecahydrospiro[5*H*,11*H*-1,3-dioxino[5,4-*c*]oxacyclotetradecin-2,2′-pyrane]-5,11-dione (erythromycin E),



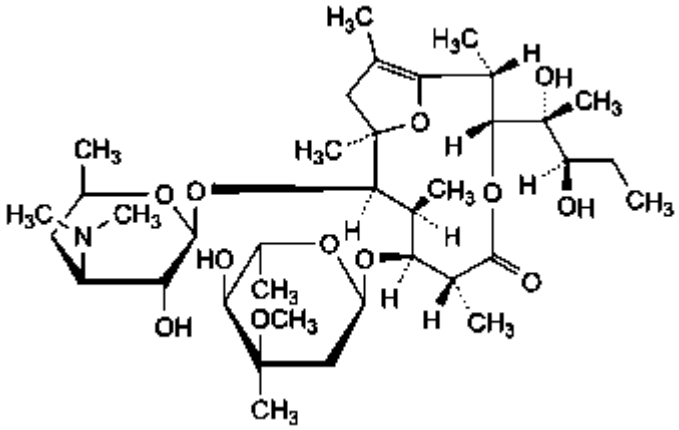
D. (1*S*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadecan-7-one (anhydroerythromycin A),



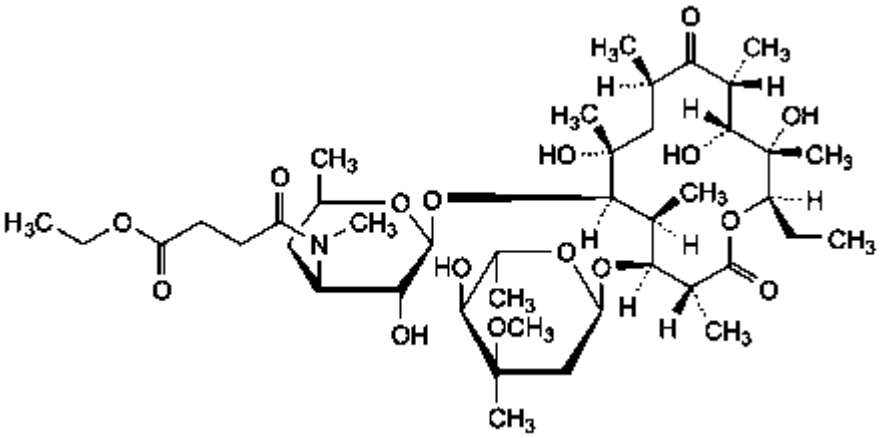
E. (2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-en-7-one (erythromycin A enol ether),

www.webofpharma.com

https://thuocngocanh.com/



F. (2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one (pseudoerythromycin A enol ether),



G. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-[(4-ethoxy-4-oxobutanoyl)methylamino]-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethyl-3″-*N*-(ethoxysuccinyl)erythromycin A).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin Ethyl Succinate Oral Suspension

General Notices

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin Ethyl Succinate Oral Suspension is a suspension of Erythromycin Ethyl Succinate in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

For the following tests prepare the oral suspension as directed on the label. The suspension examined immediately after preparation, unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

IDENTIFICATION

Dilute a quantity of the oral suspension containing the equivalent of 0.1 g of erythromycin to 25 mL with *water* and extract with two 10 mL quantities of *dichloromethane*. Wash the combined extracts with five 10 mL quantities of *water*, filter using silicone-treated filter paper (Phase Separator paper is suitable) and evaporate to dryness. The residue, after drying at 105° for 15 minutes complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of erythromycin ethyl succinate *(RS 125)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 1 volume of a 15% w/v solution of *ammonium acetate* previously adjusted to pH 7.0, 15 volumes of *ethanol (96%)* and 85 volumes of *chloroform* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) dissolve a quantity of the residue in *acetone* to produce a solution containing the equivalent of 0.1% w/v of erythromycin. Solution (2) contains 0.1% w/v of *erythromycin ethylsuccinate EPCRS* in *acetone*. Solution (3) contains 0.1% w/v of *erythromycin ethylsuccinate EPCRS* and 0.1% w/v of *erythromycin estolate EPCRS* in *acetone*. After removal of the plate, allow it to dry in air, spray with *anisaldehyde solution*, heat at 110° for 5 minutes and allow to cool. The principal spot in the chromatogram obtained with solution (1) is similar in position and colour to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

TESTS

Acidity or alkalinity

pH, 6.5 to 9.5, Appendix V L.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

To a weighed quantity of the oral suspension containing the equivalent of 0.25 g of erythromycin add 10 mL of *water* and swirl to mix. Add 200 mL of *methanol*, shake for 1 hour and dilute to 500 mL with *methanol*. Dilute 10 mL to 100 mL with *phosphate buffer pH 8.0*, stand at room temperature for 16 hours and carry out the *microbiological assay of antibiotics* for erythromycin, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

Calculate the content of erythromycin in the oral suspension taking each 1000 IU found to be equivalent to 1 mg of erythromycin. When freshly constituted the lower fiducial limit of error is not more than 120.0% of the stated amount and when stored at the temperature and for the period stated on the label during which the oral suspension may be expected to be satisfactory for use, the upper fiducial limit of error is not less than 90.0% of the stated content.

STORAGE

The oral suspension should be stored at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of erythromycin.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin Ethyl Succinate Tablets

General Notices

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin Ethyl Succinate Tablets contain Erythromycin Ethyl Succinate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of erythromycin with 20 mL of a mixture of equal volumes of *chloroform* and *methanol* for 15 minutes. Centrifuge and evaporate the upper layer to dryness. Dissolve the residue in a minimum volume of *dichloromethane*, evaporate to dryness and dry at 105° for 15 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of erythromycin ethyl succinate *(RS 125)*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) is similar in position and colour to that in the chromatogram obtained with solution (3).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of erythromycin with 25 mL of a mixture of equal volumes of *chloroform* and *methanol* for 15 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 4 volumes with a mixture of equal volumes of *chloroform* and *methanol*.

(3) 0.1% w/v of *erythromycin ethylsuccinate EPCRS* in *acetone*.

(4) 0.1% w/v of *erythromycin ethylsuccinate EPCRS* and 0.1% w/v of *erythromycin estolate EPCRS* in *acetone*.

(5) 0.020% w/v of *erythromycin BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use *silica gel G* as the coating substance.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate allow it to dry in air, spray with *anisaldehyde solution*, heat at 110° for 5 minutes and allow to cool.

www.webofpharma.com

https://thietbiuocngocanh.com/

MOBILE PHASE

1 volume of a 15% w/v solution of *ammonium acetate*, previously adjusted to pH 7.0, 15 volumes of *ethanol (96%)* and 85 volumes of *chloroform* as the mobile phase.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated spots.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (5) (5%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powdered tablets containing the equivalent of 0.25 g of erythromycin add 200 mL of *methanol*, shake for 1 hour and dilute to 500 mL with *methanol*. Dilute 10 mL to 100 mL with *phosphate buffer pH 8.0*, stand at room temperature for 16 hours and carry out the *microbiological assay of antibiotics* for erythromycin, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

Calculate the content of erythromycin in the tablets taking each 1000 IU found to be equivalent to 1 mg of erythromycin. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated content.

STORAGE

Erythromycin Ethyl Succinate Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of erythromycin.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin Gastro-resistant Capsules

General Notices

Gastro-resistant Erythromycin Capsules

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin Gastro-resistant Capsules contain Erythromycin. They are manufactured using gastro-resistant capsule shells or prepared by filling capsules with granules or particles covered with a gastro-resistant coating.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)

90.0 to 110.0% of the stated amount of Erythromycin.

IDENTIFICATION

Shake a quantity of the mixed capsule contents containing 0.1 g of Erythromycin with 5 mL of *dichloromethane*, decolourise, if necessary, with *activated charcoal*, filter through a 0.45-µm PTFE filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, after drying *in vacuo* at 60° for 10 minutes, is concordant with the *reference spectrum* of erythromycin *(RS 123)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A A solution containing 0.68% w/v of *potassium dihydrogen orthophosphate* and 0.09% w/v of *sodium hydroxide* in water. Adjust the solution to pH 6.8, if necessary, using *orthophosphoric acid* or *sodium hydroxide*.

First stage

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of 0.06M *hydrochloric acid*, at a temperature of 37° as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

After 1 hour remove the basket from the dissolution medium, and immediately lower the basket into the second dissolution medium. Discard the first medium.

Final stage

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37° as the medium.

PROCEDURE

After 1 hour remove the basket from the dissolution medium. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, in solution A. *Prepare the solutions immediately before use and protect from light.*

(1) Withdraw a sample of the second medium and filter. Use the filtered medium, diluted with solution A, if necessary, to produce a solution expected to contain 0.028% w/v of Erythromycin.

(2) 0.028% w/v of *erythromycin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under related substances may be used with isocratic elution using mobile phase A. Continue the chromatography for twice the retention time of erythromycin A.

When the chromatograms are recorded under the prescribed conditions, the retention time of erythromycin A is about 23 minutes.

DETERMINATION OF CONTENT

Calculate the content of erythromycin A, $C_{37}H_{67}NO_{13}$ in the medium using the declared content of $C_{37}H_{67}NO_{13}$ in *erythromycin BPCRS*.

The amount of erythromycin A released in the final stage is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B. *Prepare the solutions immediately before use and protect from light.*

Solution B 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Disperse a sufficient quantity of contents of the capsules in solution B and dilute to produce a solution containing 0.4% of w/v erythromycin and filter (0.45µm GF/C filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

(4) 0.4% w/v of *erythromycin for impurity M identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6) mm packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (X-Terra RP18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 65°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 35 volumes of *acetonitrile R1* and 60 volumes of *water*.

Mobile phase B 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 50 volumes of *acetonitrile R1* and 45 volumes of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-44	100	0	isocratic
44-46	100→0	0→100	linear gradient
46-61	0	100	isocratic
61-63	0→100	100→0	linear gradient
63-80	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to erythromycin A (retention time about 23 minutes) are: impurity H, about 0.3; impurity A, about 0.4; impurity B, about 0.5; erythromycin C, about 0.55; impurity M, about 0.58; impurity L, about 0.63; impurity C, about 0.9; impurity D, about 1.6; erythromycin B, about 1.75; impurity F, about 1.8 and impurity E, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

LIMITS

Identify any peaks corresponding to impurities D, E, F and L in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the corresponding correction factors: impurity D, 2.0; impurity E, 0.08;

www.webofpharma.com

https://thuocngocanh.com/

impurity F, 0.08; impurity L, 0.11.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity A or B is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (2% of each);

the area of any peak corresponding to impurity D, E, F, H or M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak corresponding to impurity L is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak*, other than the peaks due to erythromycin B and C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any *secondary peaks*, other than the peaks due to erythromycin B and C is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peak due to erythromycin B and erythromycin C and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%).

The content of each of erythromycin B and erythromycin C, as determined under Assay, is not more than 5%.

Water

The contents of the capsules contain not more than 7.5% w/w of water, Appendix IX C, using 10% w/v of *imidazole* in *methanol* in the titration vessel.

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B. *Prepare the solutions immediately before use and protect from light.*

Solution B 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Disperse a quantity of the contents of the capsules by shaking with solution B and dilute to produce a solution containing 0.4% w/v Erythromycin and filter.

(2) 0.4% w/v of *erythromycin BPCRS*.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

DETERMINATION OF CONTENT

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatograms obtained with solutions (1) and (2) and the declared contents of $C_{37}H_{67}NO_{13}$, $C_{37}H_{67}NO_{12}$ and $C_{36}H_{65}NO_{13}$ respectively in *erythromycin BPCRS*.

STORAGE

Erythromycin Gastro-resistant Capsules should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Erythromycin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin Gastro-resistant Tablets

General Notices

Erythromycin Tablets

Gastro-resistant Erythromycin Tablets

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin Gastro-resistant Tablets contain Erythromycin. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)

90.0 to 110.0% of the stated amount of Erythromycin.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.1 g of Erythromycin with 5 mL of *dichloromethane*, decolourise, if necessary, with *activated charcoal*, filter through a 0.45-µm PTFE filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, after drying *in vacuo* at 60° for 10 minutes, is concordant with the *reference spectrum* of erythromycin *(RS 123)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A A solution containing 0.68% w/v of *potassium dihydrogen orthophosphate* and 0.09% w/v of *sodium hydroxide* in water. Adjust the solution to pH 6.8, if necessary, using *orthophosphoric acid* or *sodium hydroxide*.

First stage

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of 0.06M *hydrochloric acid*, at a temperature of 37° as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

PROCEDURE

After 1 hour remove the basket from the dissolution medium, and immediately lower the basket into the second dissolution medium.

Final stage

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37°.

PROCEDURE

After 1 hour remove the basket from the dissolution medium. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, in solution A. *Prepare the solutions immediately before use and protect from light.*

(1) Withdraw a sample of the second medium and filter. Use the filtered medium, diluted with solution A, if necessary, to produce a solution expected to contain 0.028% w/v of erythromycin.

(2) 0.028% w/v of erythromycin BPCRS.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used with isocratic elution using mobile phase A. Continue the chromatography for twice the retention time of erythromycin A.

When the chromatograms are recorded under the prescribed conditions, the retention time of erythromycin A is about 23 minutes.

DETERMINATION OF CONTENT

Calculate the content of erythromycin A, $C_{37}H_{67}NO_{13}$, using the declared content of $C_{37}H_{67}NO_{13}$ in *erythromycin BPCRS*.

The amount of erythromycin A released in the final stage is not less than 75% of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B. *Prepare the solutions immediately before use and protect from light.*

Solution B 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Dissolve a quantity of powdered tablets in solution B and dilute to produce a solution containing 0.4% w/v erythromycin.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

(4) 0.4% w/v of *erythromycin for impurity M identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (X-Terra RP18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 65°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 35 volumes of *acetonitrile R1* and 60 volumes of *water*.

Mobile phase B 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 50 volumes of *acetonitrile R1* and 45 volumes of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-44	100	0	isocratic
44-46	100→0	0→100	linear gradient
46-61	0	100	isocratic
61-63	0→100	100→0	linear gradient
63-80	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to erythromycin A (retention time about 23 minutes) are: impurity H, about 0.3; impurity A, about 0.4; impurity B, about 0.5; erythromycin C, about 0.55; impurity M, about 0.58; impurity L, about 0.63; impurity C, about 0.9; impurity D, about 1.6; erythromycin B, about 1.75; impurity F, about 1.8 and impurity E, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

LIMITS

Identify any peaks corresponding to impurities D, E, F and L in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the corresponding correction factors: impurity D, 2.0; impurity E, 0.08; impurity F, 0.08; impurity L, 0.11.

www.webofpharma.com

https://thatuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity A or B is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (2% of each);

the area of any peak corresponding to impurity D, E, F, H or M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak corresponding to impurity L is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak*, other than the peaks due to erythromycin B and C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any *secondary peaks*, other than the peaks due to erythromycin B and C is not greater than 7 times the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peak due to erythromycin B and erythromycin C and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%).

The content of each of erythromycin B and erythromycin C, as determined under Assay, is not more than 5%.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B. *Prepare the solutions immediately before use and protect from light.*

Solution B 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Dissolve a quantity of the powdered tablets with solution B and dilute to produce a solution containing 0.4% w/v erythromycin.
(2) 0.4% w/v of *erythromycin BPCRS*.
(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

www.webofpharma.com

https://thuocngocanh.com/

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

DETERMINATION OF CONTENT

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatograms obtained with solutions (1) and (2) and the declared contents of $C_{37}H_{67}NO_{13}$, $C_{37}H_{67}NO_{12}$ and $C_{36}H_{65}NO_{13}$ respectively in *erythromycin BPCRS*.

STORAGE

Erythromycin Gastro-resistant Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Erythromycin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

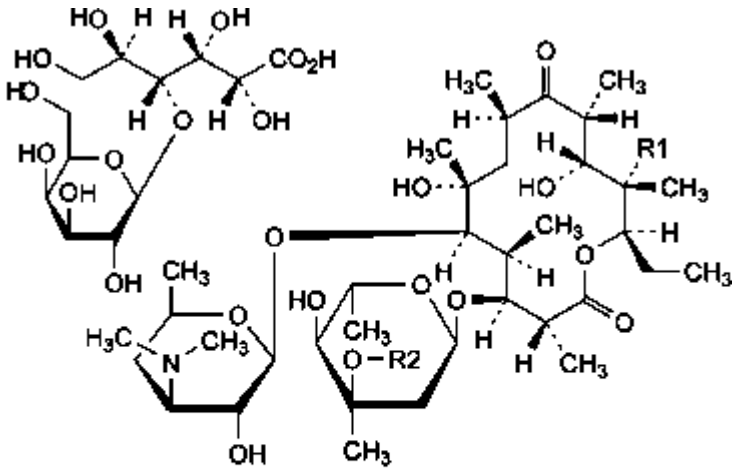
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Erythromycin Lactobionate

General Notices

(Ph. Eur. monograph 1098)



Erythromycin (lactobionate)	Mol. Formula	M_r	R1	R2
A	$C_{49}H_{89}NO_{25}$	1092	OH	CH_3
B	$C_{49}H_{89}NO_{24}$	1076	H	CH_3
C	$C_{48}H_{87}NO_{25}$	1078	OH	H

Action and use

Macrolide antibacterial.

Preparation

Erythromycin Lactobionate for Infusion

Ph Eur

DEFINITION

Mixture of the lactobionate salts of erythromycin.

Main component (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione 4-*O*-β-D-galactopyranosyl-D-gluconate (erythromycin A lactobionate).

www.webofpharma.com

https://thuocngocanh.com/

Salt of a product obtained by fermentation using a strain of *Streptomyces erythreus*.

Content

— *sum of erythromycins A, B and C expressed as lactobionates*: 93.0 per cent to 102.0 per cent (anhydrous substance);

— *erythromycin B lactobionate*: maximum 5.0 per cent (anhydrous substance);

— *erythromycin C lactobionate*: maximum 5.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly yellow, hygroscopic powder.

Solubility

Soluble in water, freely soluble in anhydrous ethanol and in methanol, very slightly soluble in acetone and in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *erythromycin lactobionate CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 1.0 g in 20 mL of *water R*.

pH (2.2.3)

6.5 to 7.5.

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Solution A Dissolve 11.5 g of *dipotassium hydrogen phosphate R* in 900 mL of *water R*, adjust to pH 8.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture *methanol R*, solution A (40:60 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 60.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 40.0 mg of *erythromycin A CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *erythromycin B CRS* and 10.0 mg of *erythromycin C CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 4 mg of *erythromycin for system suitability CRS* (containing impurities A, B, C, D, E, F, H and L) in the solvent mixture and dilute to 1 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (3.5 µm);

— *temperature*: 65 °C; preheating the mobile phase may be required, for instance by extending the inlet tubing in the oven to 30 cm.

Mobile phase:

— *mobile phase A*: *phosphate buffer solution pH 7.0 R7*, *acetonitrile R1*, *water for chromatography R* (5:35:60 *V/V/V*);

— *mobile phase B*: *phosphate buffer solution pH 7.0 R7*, *water for chromatography R*, *acetonitrile R1* (5:45:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	100	0
t_R - (t_R + 2)	100 → 0	0 → 100
(t_R + 2) - (t_R + 15)	0	100

t_R = retention time of erythromycin B, determined by injecting 10 µL of reference solution (b) and eluting with mobile phase A

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 4 °C.

Injection 100 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *erythromycin for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, E, F, H and L; use the chromatogram obtained with reference solution (b) to identify the peaks due to erythromycins B and C.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to erythromycin A (retention time = about 23 min): impurity H = about 0.3; impurity A = about 0.4; impurity B = about 0.5; erythromycin C = about 0.55; impurity L = about 0.63; impurity C = about 0.9; impurity D = about 1.61; erythromycin B = about 1.75; impurity F = about 1.81; impurity E = about 2.3.

System suitability Reference solution (d):

— *resolution*: minimum 1.2 between the peaks due to impurity B and erythromycin C;

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B; minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A. If necessary, adjust the concentration of *acetonitrile R1* in the mobile phases and/or the gradient to obtain the required separation.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 2; impurity E = 0.08; impurity F = 0.08; impurity L = 0.11;

— for each impurity, use the concentration of erythromycin A in reference solution (c).

Limits:

— *impurity C*: maximum 3.0 per cent;

— *impurities A, B*: for each impurity, maximum 2.0 per cent;

— *impurities D, E, F, H*: for each impurity, maximum 1.0 per cent;

— *impurity L*: maximum 0.4 per cent;

— *any other impurity*: for each impurity, maximum 0.4 per cent;

— *total*: maximum 7.0 per cent;

— *reporting threshold*: 0.2 per cent; disregard the peaks due to erythromycins B and C.

Free lactobionic acid

Maximum 1.0 per cent of $C_{12}H_{22}O_{12}$ (anhydrous substance).

Dissolve 0.400 g in 50 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Calculate the volume of *0.1 M sodium hydroxide* required per gram of the substance to be examined (n_1 mL). Dissolve 0.500 g in 40 mL of *anhydrous acetic acid R* and titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Calculate the volume of *0.1 M perchloric acid* required per gram of the substance to be examined (n_2 mL).

Calculate the percentage content of $C_{12}H_{22}O_{12}$ using the following expression:

www.webofpharma.com

https://thuocngocanh.com/

$$3.580\,(n_1 - n_2)$$

Water (*2.5.12*)

Maximum 5.0 per cent, determined on 0.200 g.

Use a 100 g/L solution of *imidazole R* in *anhydrous methanol R* as the solvent.

Sulfated ash (*2.4.14*)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solutions (a) and (b).

System suitability Reference solution (a):

— *symmetry factor*: maximum 2.5 for the peak due to erythromycin A;

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$) using the chromatogram obtained with reference solution (a). Calculate the percentage contents of erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatogram obtained with reference solution (b).

Express the result as erythromycin A lactobionate, erythromycin B lactobionate and erythromycin C lactobionate by multiplying the percentage content of erythromycin A by 1.4877, the percentage content of erythromycin B by 1.4986 and the percentage content of erythromycin C by 1.4972.

For the calculation of content of erythromycin lactobionate, use the sum of erythromycins A, B and C expressed as lactobionates as described above.

STORAGE

In an airtight container, protected from light. If the substance is sterile, the container is also sterile and tamper-evident.

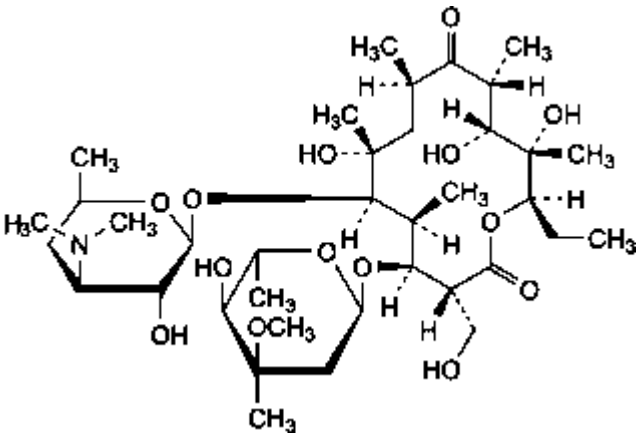
IMPURITIES

Specified impurities *A, B, C, D, E, F, H, L.*

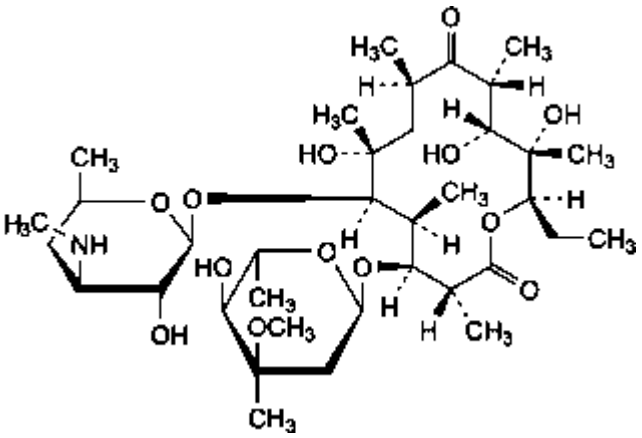
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *I, J, K, M, N.*

www.webofpharma.com

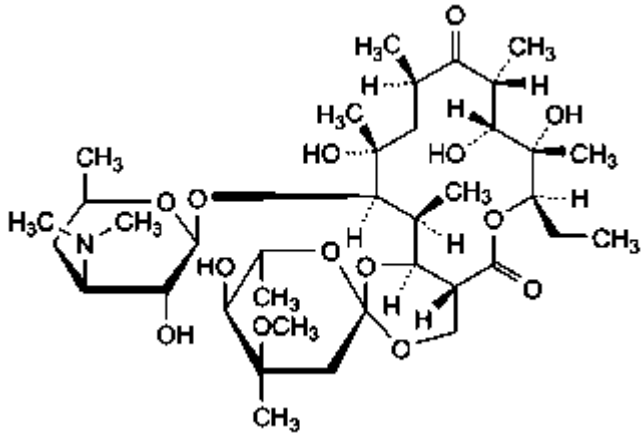
https://thuocngocanh.com/



A. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin F),



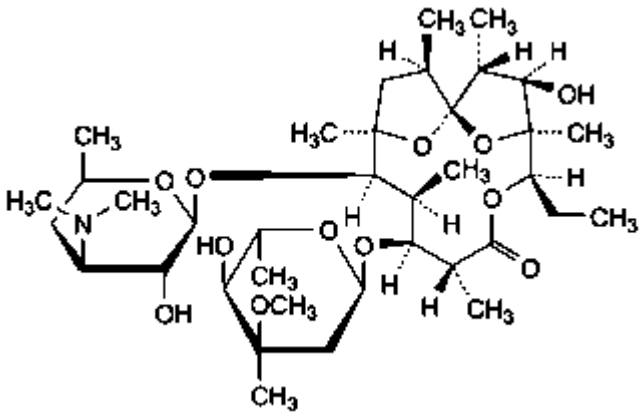
B. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(methylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethylerythromycin A),



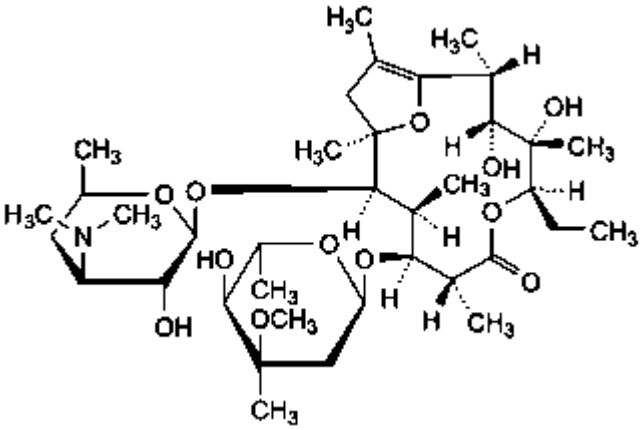
C. (2*S*,4a*R*,4′*R*,5′*S*,6′*S*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,15*R*,16*S*,16a*S*)-7-ethyl-5′,8,9,14-tetrahydroxy-4′-methoxy-4′,6′,8,10,12,14,16-heptamethyl-15-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]hexadecahydrospiro[5*H*,11*H*-1,3-dioxino[5,4-*c*]oxacyclotetradecin-2,2′-pyrane]-5,11-dione (erythromycin E),

www.webofpharma.com

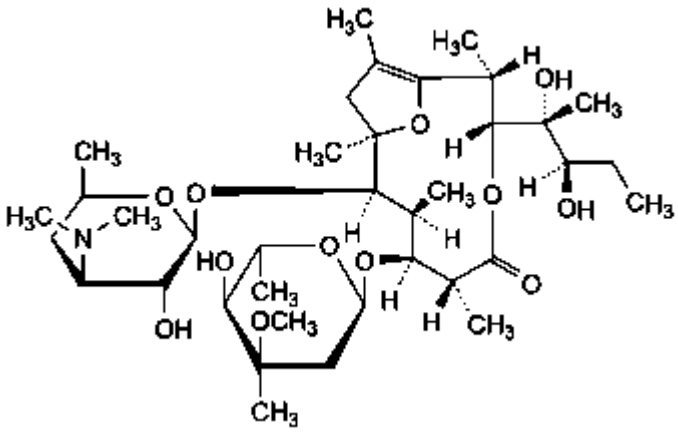
https://thuocngocanh.com/



D. (1*S*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadecan-7-one (anhydroerythromycin A),



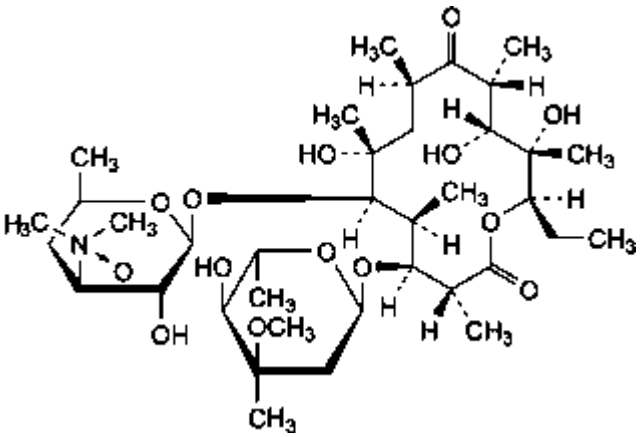
E. (2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-en-7-one (erythromycin A enol ether),



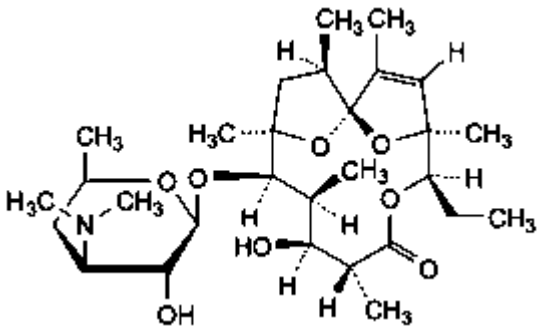
F. (2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one (pseudoerythromycin A enol ether),

www.webofpharma.com

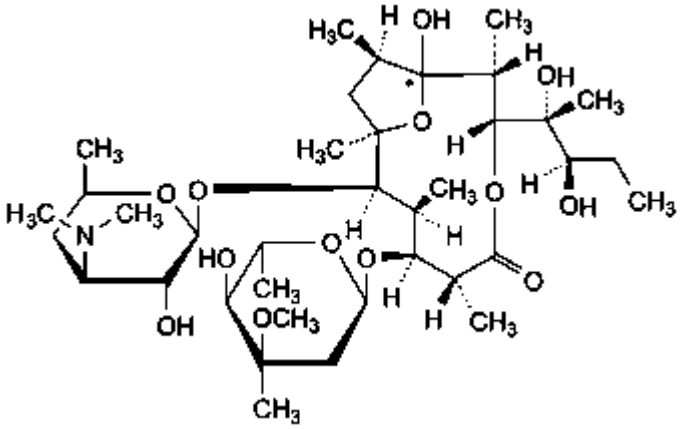
https://thuocngocanh.com/



H. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione *N*-oxide (erythromycin A 3″-*N*-oxide),



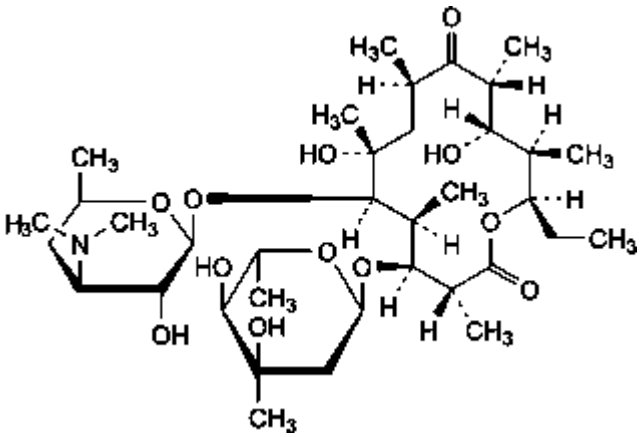
I. (1*S*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-5-ethyl-9-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadec-2-en-7-one (erythralosamine),



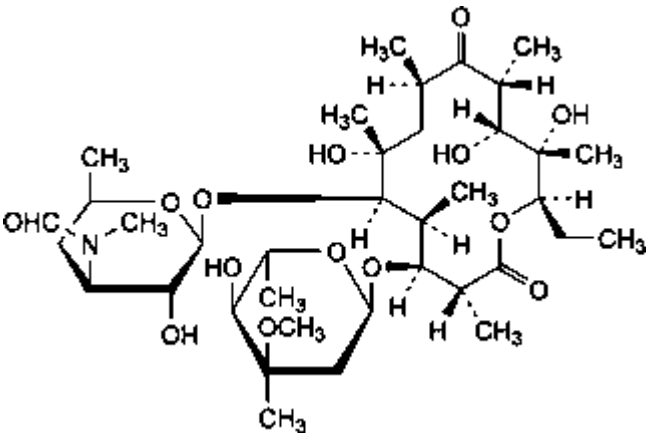
J. (1*RS*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-1-hydroxy-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridecan-5-one (pseudoerythromycin A hemiketal),

www.webofpharma.com

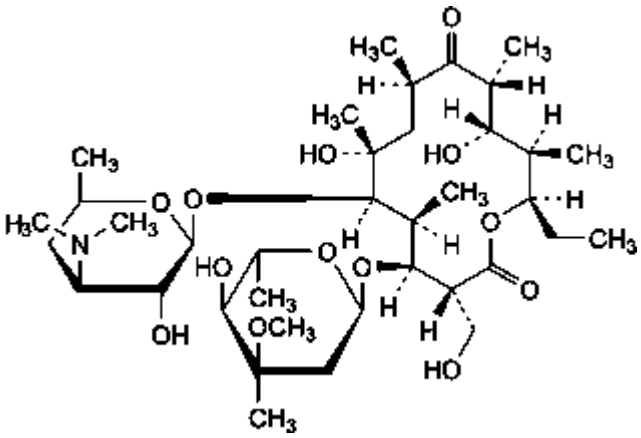
https://thuocngocanh.com/



K. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin D),



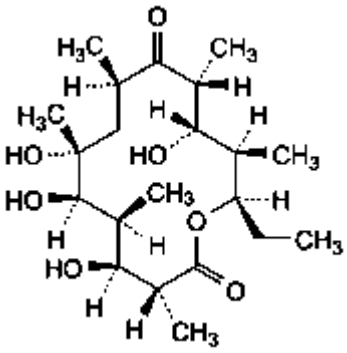
L. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(formylmethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethyl-3″-*N*-formylerythromycin A),



M. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin G),

www.webofpharma.com

https://thuocngocanh.com/



N. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-14-ethyl-4,6,7,12-tetrahydroxy-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione (erythronolide B).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin Lactobionate for Infusion

General Notices

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin Lactobionate for Infusion is a sterile material consisting of Erythromycin Lactobionate with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)

95.0 to 110.0% of the stated amount of erythromycin.

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, of the dry powder, is concordant with the *reference spectrum* of erythromycin lactobionate *(RS 126)*.

TESTS

Acidity or alkalinity

pH of a solution containing the equivalent of 1.34% w/v of erythromycin, 6.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A. *Prepare the solutions immediately before use and protect from light.*

Solution A 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol R1*.

(1) Dissolve a quantity of the contents of a sealed container to produce a solution containing the equivalent of 0.4% w/v erythromycin.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (X-Terra RP18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 65°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 35 volumes of *acetonitrile R1* and 60 volumes of *water*.

Mobile phase B 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 50 volumes of *acetonitrile R1* and 45 volumes of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-44	100	0	isocratic
44-46	100→0	0→100	linear gradient
46-61	0	100	isocratic
61-63	0→100	100→0	linear gradient
63-80	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to erythromycin A (retention time about 23 minutes) are: impurity A, about 0.4; impurity B, about 0.5; erythromycin C, about 0.55; impurity L, about 0.63; impurity C, about 0.9; impurity D, about 1.6; erythromycin B, about 1.75; impurity F, about 1.8 and impurity E, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

Identify any peaks corresponding to impurities D, E, F and L in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the corresponding correction factors: impurity D, 2.0; impurity E, 0.08; impurity F, 0.08; impurity L, 0.11.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity A or B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2% of each);

the area of any peak corresponding to impurity D, E or F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak corresponding to impurity L is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak*, other than the peaks due to erythromycin B and C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any *secondary peaks*, other than the peaks due to erythromycin B and C is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peak due to erythromycin B and erythromycin C and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%).

The content of each of erythromycin B and erythromycin C, as determined under Assay, is not more than 5%.

ASSAY

Determine the weight of the contents of 10 sealed containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A. *Prepare the solutions immediately before use and protect from light.*

Solution A 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol R1*.

(1) Dilute a quantity of the mixed contents of sealed containers to produce a solution containing the equivalent of 0.4% w/v of Erythromycin.
(2) 0.4% w/v of *erythromycin BPCRS*.
(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

www.webofpharma.com

https://thietbiuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

DETERMINATION OF CONTENT

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatograms obtained with solutions (1) and (2) and the declared contents of $C_{37}H_{67}NO_{13}$, $C_{37}H_{67}NO_{12}$ and $C_{36}H_{65}NO_{13}$ respectively in *erythromycin BPCRS*.

LABELLING

The label of the sealed container states the quantity of active ingredient contained in it in terms of the equivalent amount of erythromycin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Erythromycin Lactobionate.

© Crown Copyright 2022

www.webofpharma.com

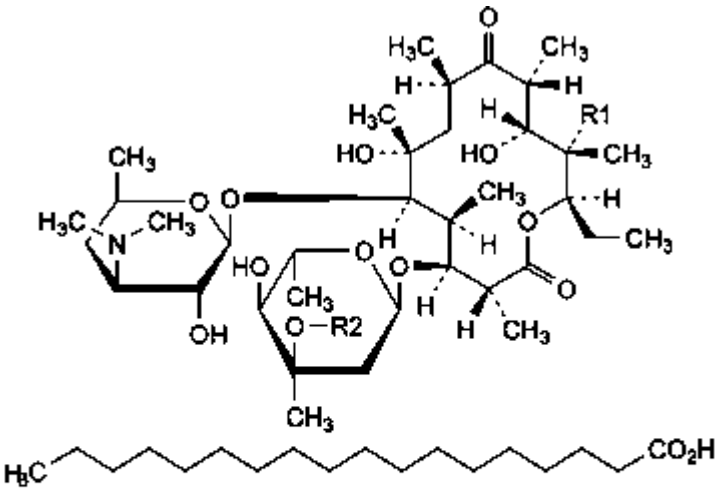
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Erythromycin Stearate

General Notices

(Ph. Eur. monograph 0490)



Erythromycin (stearate)	Mol. Formula	M_r	R1	R2
A	$C_{55}H_{103}NO_{15}$	1018	OH	CH_3
B	$C_{55}H_{103}NO_{14}$	1002	H	CH_3
C	$C_{54}H_{101}NO_{15}$	1004	OH	H

Action and use

Macrolide antibacterial.

Preparation

Erythromycin Stearate Tablets

Ph Eur

DEFINITION

Mixture of the stearate salts of erythromycin and stearic acid.

Main component (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione octadecanoate (erythromycin A stearate).

www.webofpharma.com

https://thuocngocanh.com/

Salt of a product obtained by fermentation using a strain of *Streptomyces erythreus*.

Content

— *sum of erythromycins A, B and C expressed as stearates*: 79.0 per cent to 102.0 per cent (anhydrous substance);

— *erythromycin B stearate*: maximum 5.0 per cent (anhydrous substance);

— *erythromycin C stearate*: maximum 5.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone and in methanol.

Solutions may be opalescent.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *erythromycin stearate CRS*.

TESTS

Free stearic acid

Maximum 14.0 per cent (anhydrous substance) of $C_{18}H_{36}O_2$.

Dissolve 0.400 g in 50 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). Calculate the volume of *0.1 M sodium hydroxide* required per gram of the substance to be examined (n_1 mL). Dissolve 0.500 g in 30 mL of *methylene chloride R*. If the solution is opalescent, filter and shake the residue with 3 quantities, each of 25 mL, of *methylene chloride R*. Filter, if necessary, and rinse the filter with *methylene chloride R*. Reduce the volume of the combined filtrate and rinsings to 30 mL by evaporation on a water-bath. Add 50 mL of *glacial acetic acid R* and titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20). Calculate the volume of *0.1 M perchloric acid* required per gram of the substance to be examined (n_2 mL).

Calculate the percentage content of $C_{18}H_{36}O_2$ using the following expression:

$$2.845\left(n_1 - n_2\right) \times \frac{100}{100 - h}$$

h = percentage water content.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Solution A Dissolve 11.5 g of *dipotassium hydrogen phosphate R* in 900 mL of *water R*, adjust to pH 8.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*.

Solvent mixture *methanol R*, solution A (40:60 *V/V*).

Test solution Dissolve 55.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Centrifuge and use the clear solution.

Reference solution (a) Dissolve 40.0 mg of *erythromycin A CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *erythromycin B CRS* and 10.0 mg of *erythromycin C CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 4 mg of *erythromycin for system suitability CRS* (containing impurities A, B, C, D, E, F, H and L) in the solvent mixture and dilute to 1 mL with the solvent mixture.

Reference solution (e) Dissolve 4 mg of *erythromycin stearate for impurity S identification CRS* in the solvent mixture and dilute to 1 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (3.5 µm);

— *temperature*: 65 °C; preheating the mobile phase may be required, for instance by extending the inlet tubing in the oven to 30 cm.

Mobile phase:

— *mobile phase A*: *phosphate buffer solution pH 7.0 R7*, *acetonitrile R1*, *water for chromatography R* (5:35:60 *V/V/V*);

— *mobile phase B*: *phosphate buffer solution pH 7.0 R7*, *water for chromatography R*, *acetonitrile R1* (5:45:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - t_R	100	0
t_R - (t_R + 2)	100 → 0	0 → 100
(t_R + 2) - (t_R + 15)	0	100

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)

t_R = retention time of erythromycin B, determined by injecting 10 µL of reference solution (b) and eluting with mobile phase A

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Autosampler Set at 4 °C.

Injection 100 µL.

Identification of impurities Use the chromatogram supplied with *erythromycin for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, E, F and L; use the chromatogram supplied with *erythromycin stearate for impurity S identification CRS* and the chromatogram obtained with reference solution (e) to identify the peak due to impurity S; use the chromatogram obtained with reference solution (b) to identify the peaks due to erythromycins B and C.

Relative retention With reference to erythromycin A (retention time = about 23 min): impurity A = about 0.4; impurity B = about 0.5; erythromycin C = about 0.55; impurity L = about 0.63; impurity C = about 0.9; impurity D = about 1.61; erythromycin B = about 1.75; impurity F = about 1.81; impurity S = about 2.1; impurity E = about 2.3.

System suitability Reference solution (d):

— *resolution*: minimum 1.2 between the peaks due to impurity B and erythromycin C;

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B; minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A. If necessary, adjust the concentration of *acetonitrile R1* in the mobile phases and/or the gradient to obtain the required separation.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 2; impurity E = 0.08; impurity F = 0.08; impurity L = 0.11;

— for each impurity, use the concentration of erythromycin A in reference solution (c).

Limits:

— *impurity C*: maximum 3.0 per cent;

— *impurities A, B*: for each impurity, maximum 2.0 per cent;

— *impurities D, E, F, S*: for each impurity, maximum 1.0 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *impurity L*: maximum 0.4 per cent;

— *any other impurity*: for each impurity, maximum 0.4 per cent;

— *total*: maximum 7.0 per cent;

— *reporting threshold*: 0.2 per cent; disregard the peaks due to erythromycins B and C.

Water (2.5.12)

Maximum 4.0 per cent, determined on 0.300 g.

Use a 100 g/L solution of *imidazole R* in *anhydrous methanol R* as the solvent.

Sulfated ash (2.4.14)

Maximum 0.5 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solutions (a) and (b).

System suitability Reference solution (a):

— *symmetry factor*: maximum 2.5 for the peak due to erythromycin A;

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$) using the chromatogram obtained with reference solution (a). Calculate the percentage contents of erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatogram obtained with reference solution (b).

Express the results as erythromycin A stearate, erythromycin B stearate and erythromycin C stearate by multiplying the percentage content of erythromycin A by 1.3869, the percentage content of erythromycin B by 1.3955 and the percentage content of erythromycin C by 1.3944.

For the calculation of content of erythromycin stearate, use the sum of erythromycins A, B and C expressed as stearates as described above.

STORAGE

Protected from light.

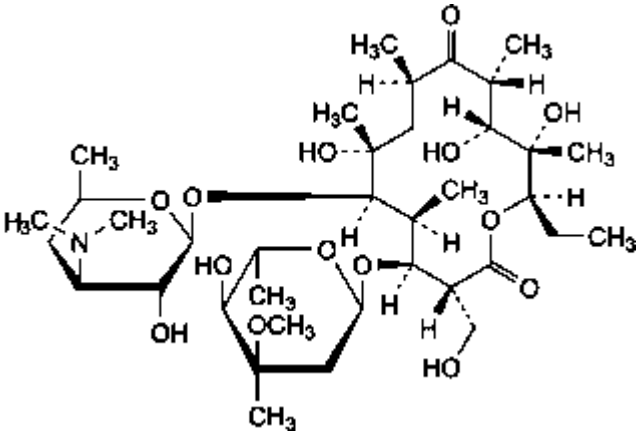
IMPURITIES

Specified impurities *A, B, C, D, E, F, L, S.*

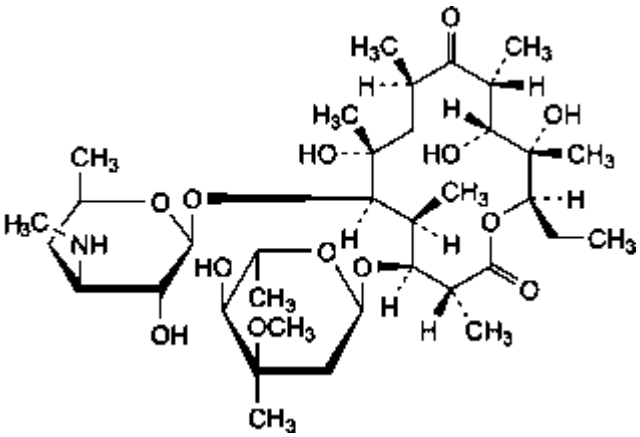
www.webofpharma.com

https://thuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H, I, J, K, M, N.*



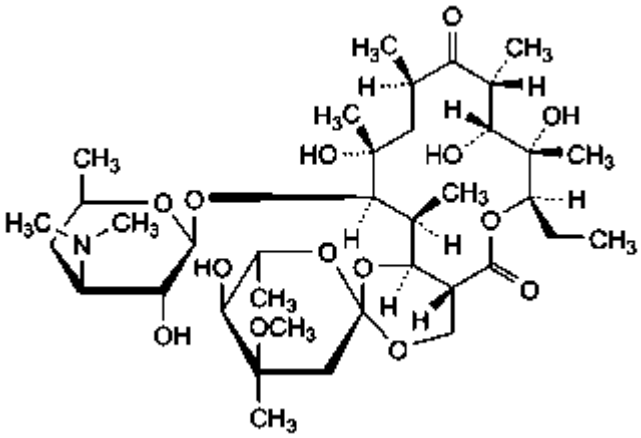
A. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin F),



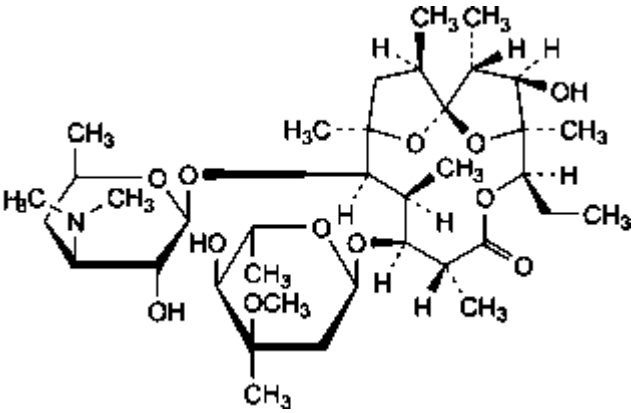
B. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(methylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethylerythromycin A),

www.webofpharma.com

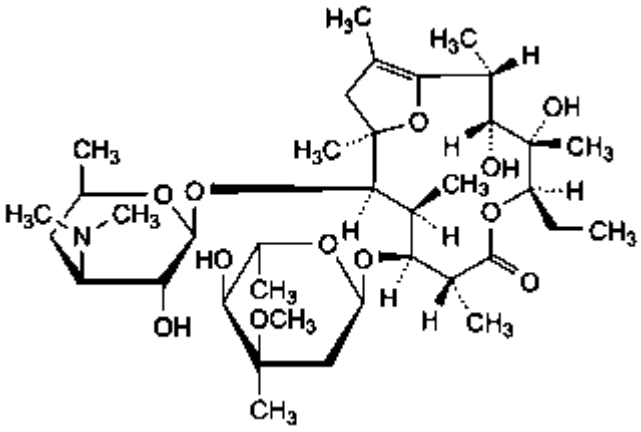
https://thuocngocanh.com/



C. (2*S*,4a*R*,4′*R*,5′*S*,6′*S*,7*R*,8*S*,9*R*,10*R*,12*R*,14*R*,15*R*,16*S*,16a*S*)-7-ethyl-5′,8,9,14-tetrahydroxy-4′-methoxy-4′,6′,8,10,12,14,16-heptamethyl-15-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]hexadecahydrospiro[5*H*,11*H*-1,3-dioxino[5,4-*c*]oxacyclotetradecin-2,2′-pyrane]-5,11-dione (erythromycin E),



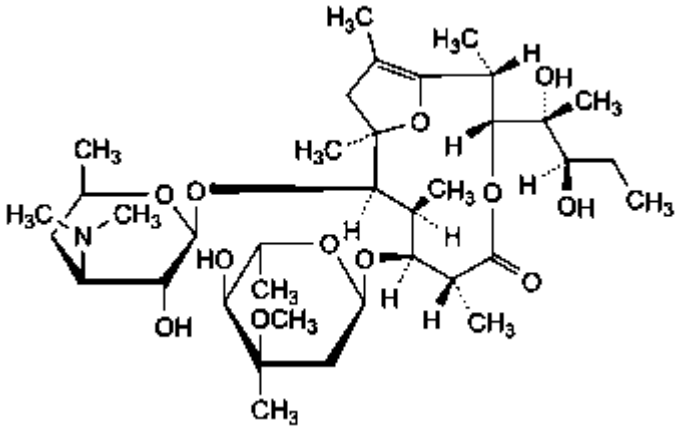
D. (1*S*,2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadecan-7-one (anhydroerythromycin A),



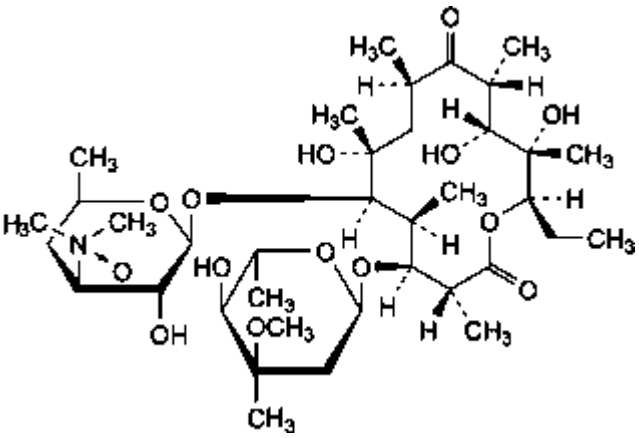
E. (2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-en-7-one (erythromycin A enol ether),

www.webofpharma.com

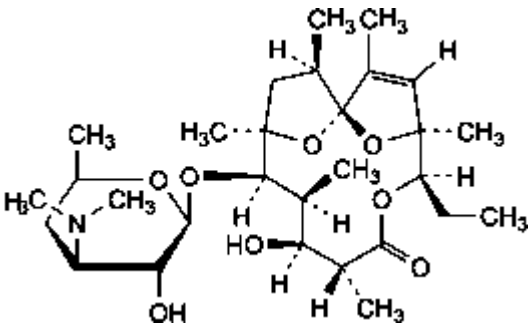
https://thuvienthuocngocanh.com/



F. (2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one (pseudoerythromycin A enol ether),



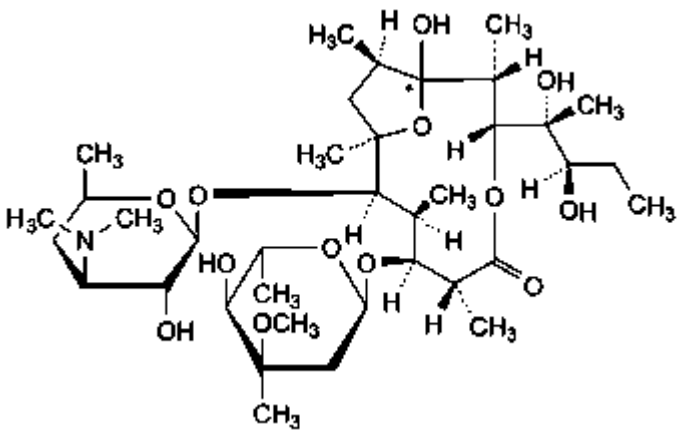
H. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione *N*-oxide (erythromycin A 3″-*N*-oxide),



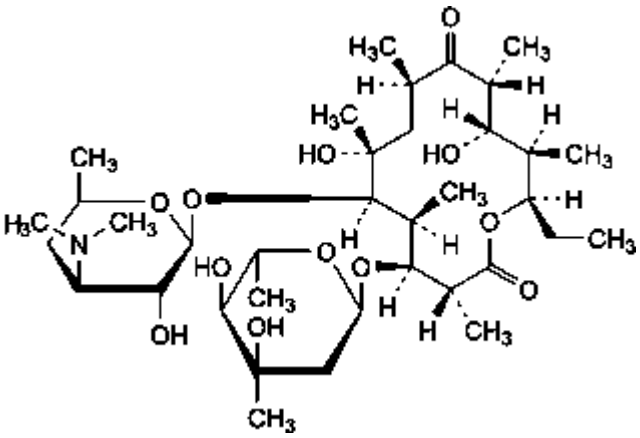
I. (1*S*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,14*R*)-5-ethyl-9-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-6,15,16-trioxatricyclo[10.2.1.1^{1,4}]hexadec-2-en-7-one (erythralosamine),

www.webofpharma.com

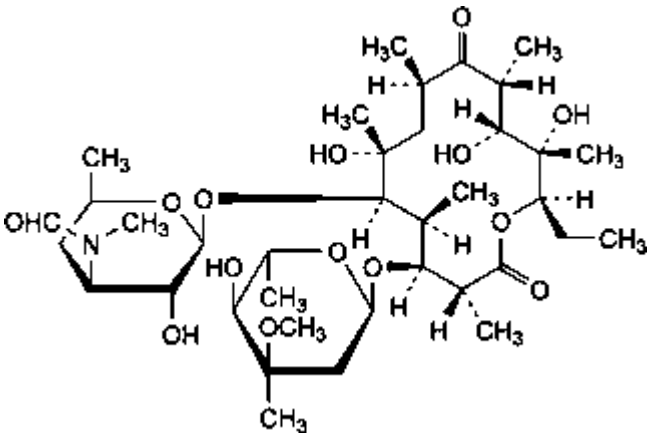
https://thuvienthuocngocanh.com/



J. (1*RS*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*)-7-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-3-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-1-hydroxy-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridecan-5-one (pseudoerythromycin A hemiketal),



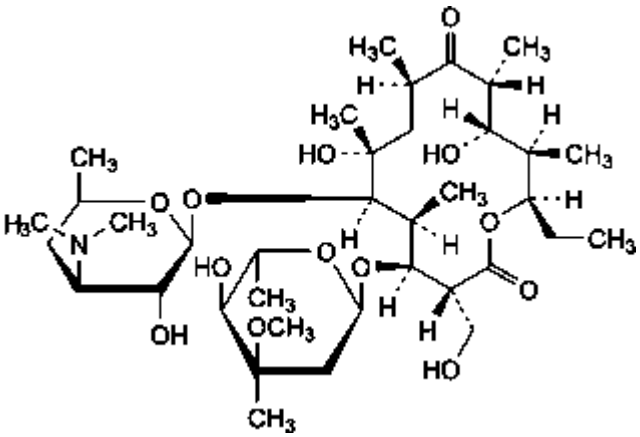
K. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin D),



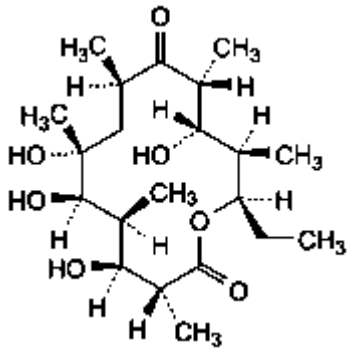
L. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(formylmethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (3″-*N*-demethyl-3″-*N*-formylerythromycin A),

www.webofpharma.com

https://thuocngocanh.com/



M. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12-dihydroxy-3-(hydroxymethyl)-5,7,9,11,13-pentamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (erythromycin G),



N. (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*S*,13*R*,14*R*)-14-ethyl-4,6,7,12-tetrahydroxy-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione (erythronolide B),

S. unknown structure.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin Stearate Tablets

General Notices

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin Stearate Tablets contain Erythromycin Stearate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)

95.0 to 105.0% of the stated amount of erythromycin.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 0.1 g of erythromycin with 10 mL of *water*, allow to settle and discard the supernatant liquid. Add 10 mL of *methanol* to the residue, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum*, Appendix II A, of the residue after drying at a pressure not exceeding 0.7 kPa is concordant with the *reference spectrum* of erythromycin stearate *(RS 127)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a 2.722% w/v solution of *sodium acetate*, adjusted to pH 5.0 with *glacial acetic acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes transfer 5 mL of a filtered sample of the medium to a graduated flask, add 40 mL of *glacial acetic acid* and 10 mL of a 0.5% w/v solution of *4-dimethylaminobenzaldehyde* in *glacial acetic acid* and dilute to 100 mL with a mixture of 35 volumes of *glacial acetic acid* and 70 volumes of *hydrochloric acid*. Allow to stand for 15 minutes and measure the absorbance of the resulting solution at the maximum at 485 nm, Appendix II B, using dissolution medium that has been subjected to the conditions of the test in the reference cell

www.webofpharma.com

https://thuocngocanh.com/

(2) Prepare a suitable solution of *erythromycin stearate BPCRS* in the dissolution medium and filter. Transfer 5 mL of the filtered solution to a graduated flask, add 40 mL of *glacial acetic acid* and 10 mL of a 0.5% w/v solution of *4-dimethylaminobenzaldehyde* in *glacial acetic acid* and dilute to 100 mL with a mixture of 35 volumes of *glacial acetic acid* and 70 volumes of *hydrochloric acid*. Allow to stand for 15 minutes and measure the *absorbance* of the resulting solution at the maximum at 485 nm, Appendix II B, using dissolution medium that has been subjected to the conditions of the test in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of erythromycins, ($C_{37}H_{67}NO_{13}$), in the medium from the absorbances obtained and using the declared content of $C_{37}H_{67}NO_{13}$ in *erythromycin stearate BPCRS*.

The amount of erythromycin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A. *Prepare the solutions immediately before use and protect from light.*

Solution A 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol R1*.

(1) Disperse a quantity of powdered tablets in solution A and shake for a minimum of 30 minutes, using ultrasound where necessary. Dilute to produce a solution containing the equivalent of 0.4% w/v of erythromycin and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.
(4) 0.4% w/v of *erythromycin stearate for impurity S identification EPCRS*.
(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (X-Terra RP18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 65°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 35 volumes of *acetonitrile R1* and 60 volumes of *water*.

Mobile phase B 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 50 volumes of *acetonitrile R1* and 45 volumes of *water*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-44	100	0	isocratic
44-46	100→0	0→100	linear gradient
46-61	0	100	isocratic
61-63	0→100	100→0	linear gradient
63-80	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to erythromycin A (retention time about 23 minutes) are: impurity A, about 0.4; impurity B, about 0.5; erythromycin C, about 0.55; impurity L, about 0.63; impurity C, about 0.9; impurity D, about 1.6; erythromycin B, about 1.75; impurity F, about 1.8; impurity S, about 2.1; impurity E, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

LIMITS

Identify any peaks corresponding to impurities D, E, F and L in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the corresponding correction factors: impurity D, 2.0; impurity E, 0.08; impurity F, 0.08; impurity L, 0.11.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity A or B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2% of each);

the area of any peak corresponding to impurity D, E, F or S is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak corresponding to impurity L is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

www.webofpharma.com

https://thuocngocanh.com/

the sum of the areas of any *secondary peaks*, other than the peaks due to erythromycin B and C is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peak due to erythromycin B and erythromycin C and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%).

The content of each of erythromycin B and erythromycin C, as determined under Assay, is not more than 5%.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A. *Prepare the solutions immediately before use and protect from light.*

Solution A 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol R1*.

(1) Dissolve a quantity of the powdered tablets in solution A and shake for a minimum of 30 minutes, using ultrasound where necessary. Dilute to produce a solution containing the equivalent of 0.4% w/v of erythromycin.
(2) 0.4% w/v of *erythromycin BPCRS*.
(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

DETERMINATION OF CONTENT

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatograms obtained with solutions (1) and (2) and the declared contents of $C_{37}H_{67}NO_{13}$, $C_{37}H_{67}NO_{12}$ and $C_{36}H_{65}NO_{13}$ respectively in *erythromycin BPCRS*.

STORAGE

Erythromycin Stearate Tablets should be protected from light.

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The quantity of active ingredient is stated in terms of the equivalent amount of Erythromycin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Erythromycin Stearate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythropoietin Concentrated Solution

General Notices

(Ph. Eur. monograph 1316)

The label states (1) the type of erythropoeitin using the appropriate International Nonproprietary Name (Epoetin Alfa, Epoetin Beta, etc) and (2) the approved code in lower case letters indicative of the method of production.

```
APPRLICDSR   VLERYLLEAK   EAENITTGCA   EHCSLNENIT   40
VPDTKVNFYA   WKRMEVGQQA   VEVWQGLALL   SEAVLRGQAL   80
LVNSSQPWEP   LQLHVDKAVS   GLRSLTTLLR   ALGAQKEAIS   120
PPDAASAAPL   RTITADTFRK   LFRVYSNFLR   GKLKLYTGEA   160
CRTGD                                             165
```

disulfide bridges: 7-161, 29-33

M_r approx. 30 600

Action and use

Erythropoietin analogue.

Preparation

Erythropoietin Injection

Ph Eur

DEFINITION

Solution containing a family of closely-related glycoproteins which are indistinguishable from the naturally occurring human erythropoietin (urinary erythropoietin) in terms of amino acid sequence (165 amino acids), at a concentration of 0.5-10 mg/mL. It may also contain buffer salts and other excipients. It has a potency of not less than 100 000 IU per milligram of active substance determined using the conditions described under Assay and in the test for protein.

PRODUCTION

Erythropoietin is produced in rodent cells *in vitro* by a method based on recombinant DNA (rDNA) technology. During the course of product development, it must be demonstrated that the manufacturing process consistently produces a product with the expected glycosylation pattern using suitably qualified assay(s).

Prior to batch release, the following tests are carried out on each batch of the erythropoietin concentrated solution, unless exemption has been granted by the competent authority.

www.webofpharma.com

https://thuocngocanh.com/

Host cell-derived proteins

The limit is approved by the competent authority.

Host cell- and vector-derived DNA

The limit is approved by the competent authority.

Glycan analysis

Use a suitable method developed according to general chapter *2.2.59. Glycan analysis of glycoproteins*, section 2-3:

— after desalting, release the *N*–glycans using 1 of the agents described in Table 2.2.59.-1, for example peptide *N*-glycosidase F (PNGase F);

— if needed, label the released *N*–glycans with 1 of the fluorescent labelling agents described in Table 2.2.59.-2;

— analyse the labelled or unlabelled *N*-glycans using a suitable technique.

The following procedure is given as an example.

Solution A Dissolve 0.77 g of *ammonium acetate R* in *water R* and dilute to 1000.0 mL with the same solvent.

Test solution Desalt a volume of the preparation to be examined by a suitable method (for example, using a suitable centrifugal filter) with solution A. Dilute with solution A to obtain a concentration of approximately 1 mg/mL. Add 500 U of *peptide N-glycosidase F R* per 100 µL of the obtained solution and incubate at 37 °C for at least 18 h. Evaporate the solvent completely by vacuum centrifugation at room temperature. Reconstitute the dried material by adding 80 µL *water R* per 100 µL of deglycosylated erythropoietin.

Reference solution (a) Dissolve the contents of a vial of *erythropoietin for physicochemical tests CRS* in *water R*. Desalt a volume of this preparation and carry out *N*-glycan release at the same time and in the same manner as for the test solution.

Reference solution (b) Use a suitable erythropoietin in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate consistency of production. Desalt a volume of this preparation and carry out the *N*-glycan release at the same time and in the same manner as for the test solution.

Analyse the native *N*-glycans by liquid chromatography (*2.2.29*).

A precolumn containing *strongly basic anion-exchange resin for chromatography R2* (8.5 µm), may be used.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R2* (8.5 µm);

— *temperature*: 30 °C.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: 40 g/L solution of *sodium hydroxide R*;

— *mobile phase C*: 82 g/L solution of *anhydrous sodium acetate R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 60	85 → 67	10	5 → 23
60 - 61	67 → 0	10 → 25	23 → 75
61 - 65	0	25	75
65 - 66	0 → 85	25 → 10	75 → 5
66 - 80	85	10	5

Flow rate 1.0 mL/min

Detection Electrochemical detector (pulsed amperometry).

Autosampler Set at 10 °C.

Injection 50 µL.

Identification of peaks Use the chromatogram supplied with *erythropoietin for physicochemical tests CRS* to identify the 4 peak clusters corresponding to mono- (S1), bi- (S2), tri- (S3) and tetra-sialylated (S4) *N*-glycans.

System suitability:

— the chromatogram obtained with reference solution (a) is qualitatively similar to the chromatogram supplied with *erythropoietin for physicochemical tests CRS*.

Results:

— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (b);

— the retention times of the peaks in the chromatogram obtained with the test solution correspond to those in the chromatogram obtained with reference solution (b);

— no additional peaks are observed in the chromatogram obtained with the test solution in comparison with the chromatogram obtained with reference solution (b).

Calculate the percentage contents of mono-, bi-, tri- and tetra-sialylated *N*-glycans taking into account the total relative peak area for each peak cluster with reference to the sum of the areas of all peak clusters.

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *percentage of mono-sialylated N-glycans*: as authorised by the competent authority;

— *percentage of bi-sialylated N-glycans*: as authorised by the competent authority;

— *percentage of tri-sialylated N-glycans*: as authorised by the competent authority;

— *percentage of tetra-sialylated N-glycans*: as authorised by the competent authority.

CHARACTERS

Appearance

Clear or slightly turbid, colourless solution.

IDENTIFICATION

A. It gives the appropriate response when examined using the conditions described under Assay.

B. Capillary zone electrophoresis (2.2.47).

Test solution Dilute the preparation to be examined with water R to obtain a concentration of 1 mg/mL. Desalt 0.25 mL of the solution by passage through a micro-concentrator cartridge provided with a membrane with a molecular mass cut-off of not more than 10 000 Da. Add 0.2 mL of water R to the sample and desalt again. Repeat the desalting procedure once more. Dilute the sample with water R, determine its protein concentration as described under Tests and adjust to a concentration of approximately 1 mg/mL with water R.

Reference solution Dissolve the contents of a vial of erythropoietin for physicochemical tests CRS in 0.10 mL of water R. Proceed with desalting as described for the test solution.

Capillary:

— *material*: uncoated fused silica;

— *size*: effective length = about 100 cm, Ø = 50 µm.

Temperature 35 °C.

CZE buffer concentrate (0.1 M sodium chloride, 0.1 M tricine, 0.1 M sodium acetate) Dissolve 0.584 g of sodium chloride R, 1.792 g of tricine R and 0.820 g of anhydrous sodium acetate R in water R and dilute to 100.0 mL with the same solvent.

1 M putrescine solution Dissolve 0.882 g of putrescine R in 10 mL of water R. Distribute in 0.5 mL aliquots.

CZE buffer (0.01 M tricine, 0.01 M sodium chloride, 0.01 M sodium acetate, 7 M urea, 2.5 mM putrescine) Dissolve 21.0 g of urea R in 25 mL of water R by warming in a water-bath at 30 °C. Add 5.0 mL of CZE buffer concentrate and 125 µL of 1 M putrescine solution. Dilute to 50.0 mL with water R. Using dilute acetic acid R, adjust to pH 5.55 at 30 °C and filter through a membrane filter (nominal pore size 0.45 µm).

Detection Spectrophotometer at 214 nm.

www.webofpharma.com

https://thuocngocanh.com/

Set the autosampler to store the samples at 4 °C during analysis.

Preconditioning of the capillary Rinse the capillary for 60 min with *0.1 M sodium hydroxide* filtered through a membrane filter (nominal pore size 0.45 µm) and for 60 min with CZE buffer. Apply voltage for 12 h (20 kV).

Between-run rinsing Rinse the capillary for 10 min with *water R*, for 5 min with *0.1 M sodium hydroxide* filtered through a membrane filter (nominal pore size 0.45 µm) and for 10 min with CZE buffer.

Injection Under pressure or vacuum.

Migration Apply a field strength of 143 V/cm (15.4 kV for capillaries of 107 cm total length) for 80 min, using CZE buffer as the electrolyte in both buffer reservoirs.

System suitability In the electropherogram obtained with the reference solution, a pattern of well separated peaks corresponding to the peaks in the electropherogram of erythropoietin supplied with *erythropoietin for physicochemical tests CRS* is seen, and the largest peak is at least 50 times greater than the baseline noise. If necessary, adjust the sample load to give peaks of sufficient height. Identify the peaks due to isoforms 1 to 8. Isoform 1 may not be visible. The peak due to isoform 8 is detected and the resolution between the peaks due to isoforms 5 and 6 is not less than 1. Repeat the separation at least 3 times. The baseline is stable, showing little drift, and the distribution of peaks is qualitatively and quantitatively similar to the distribution of peaks in the electropherogram of erythropoietin supplied with *erythropoietin for physicochemical tests CRS*. The relative standard deviation of the migration time of the peak due to isoform 2 is less than 2 per cent.

Limits Identify the peaks due to isoforms 1 to 8 in the electropherogram obtained with the test solution by comparison with the electropherogram obtained with the reference solution. Calculate the percentage content of each isoform from the corresponding peak area. The percentages are within the following ranges:

Isoform	Content (per cent)
1	0 - 15
2	0 - 15
3	1 - 20
4	10 - 35
5	15 - 40
6	10 - 35
7	5 - 25
8	0 - 15

C. Polyacrylamide gel electrophoresis and immunoblotting.

(a) Polyacrylamide gel electrophoresis (*2.2.31*).

Gel dimensions 0.75 mm thick, about 16 cm square.

www.webofpharma.com

https://thuocngocanh.com/

Resolving gel 12 per cent acrylamide.

Sample buffer *concentrated SDS-PAGE sample buffer R*.

Test solution (a) Dilute the preparation to be examined in *water R* to obtain a concentration of 1.0 mg/mL. To 1 volume of this solution add 1 volume of sample buffer.

Test solution (b) Dilute the preparation to be examined in *water R* to obtain a concentration of 0.1 mg/mL. To 1 volume of this solution add 1 volume of sample buffer.

Reference solution (a) Dissolve the contents of a vial of *erythropoietin for physicochemical tests CRS* in 0.10 mL of *water R*. To 1 volume of this solution add 1 volume of sample buffer.

Reference solution (b) Dissolve the contents of a vial of *erythropoietin for physicochemical tests CRS* in *water R* and dilute with the same solvent to obtain a concentration of 0.1 mg/mL. To 1 volume of this solution add 1 volume of sample buffer.

Reference solution (c) A solution of molecular mass markers suitable for calibrating SDS-polyacrylamide gels in the range of 10-70 kDa.

Reference solution (d) A solution of pre-stained molecular mass markers suitable for calibrating SDS-polyacrylamide gels in the range of 10-70 kDa and suitable for the electrotransfer to an appropriate membrane.

Sample treatment Boil for 2 min.

Application 20 µL, in the following order: reference solution (c), reference solution (a), test solution (a), empty well, reference solution (b), test solution (b), reference solution (d).

At the end of the separation, remove the gel-cassette from the apparatus and cut the gel into 2 parts: the first part containing reference solution (c), reference solution (a) and test solution (a); the second part containing reference solution (b), test solution (b) and reference solution (d).

Detection By Coomassie staining on the first part of the gel.

System suitability Reference solution (c):

— the validation criteria are met.

Results The electropherogram obtained with test solution (a) shows a single diffuse band corresponding in position and intensity to the single band seen in the electropherogram obtained with reference solution (a).

(b) Immunoblotting.

Transfer the second part of the gel onto a membrane suitable for the immobilisation of proteins, using commercially available electrotransfer equipment and following the manufacturer's instructions. After electrotransfer, incubate the membrane in a neutral isotonic buffer containing a suitable blocking agent (for example, 50 g/L of dried milk or 10 per cent *V/V* foetal calf serum), for 1-2 h, followed by incubation for 1-14 h in the same blocking solution with a suitable dilution of either a polyclonal or monoclonal anti-erythropoietin antibody. Detect erythropoietin-bound antibody using a suitable enzyme- or radiolabelled antibody (for example, an alkaline phosphatase-conjugated

www.webofpharma.com

https://thuocngocanh.com/

second antibody). The precise details of blocking agents, concentrations and incubation times should be optimised using the principles set out in general chapter (2.7.1) *Immunochemical methods*.

System suitability In the electropherogram obtained with reference solution (d), the molecular mass markers are resolved on the membrane into discrete bands, with a linear relationship between distance migrated and logarithm$_{10}$ of the molecular mass.

Results The electropherogram obtained with test solution (b) shows a single broad band corresponding in position and intensity to the single band seen in the electropherogram obtained with reference solution (b).

D. Peptide mapping (2.2.55).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Dilute the preparation to be examined in *tris acetate buffer solution pH 8.5 R* to a concentration of 1.0 mg/mL. Equilibrate the solution in *tris acetate buffer solution pH 8.5 R* using a suitable procedure (dialysis against *tris acetate buffer solution pH 8.5 R*, or membrane filtration using the procedure described under Identification B, but reconstituting the desalted sample with *tris acetate buffer solution pH 8.5 R*, are suitable). Transfer the dialysed solution to a polypropylene centrifuge tube. Freshly prepare a solution of *trypsin for peptide mapping R* at a concentration of 1 mg/mL in *water R*, and add 2 µL to 0.10 mL of the dialysed solution. Cap the tube and place in a water-bath at 37 °C for 18 h. Remove the sample from the water-bath and stop the reaction immediately by freezing.

Reference solution Dissolve the contents of a vial of *erythropoietin for physicochemical tests CRS* in 0.10 mL of *water R*. Prepare as for the test solution, ensuring that all procedures are carried out simultaneously, and under identical conditions.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (2.2.29).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase:

— *mobile phase A*: 0.06 per cent *V/V* solution of *trifluoroacetic acid R*;

— *mobile phase B*: to 100 mL of *water for chromatography R* add 0.6 mL of *trifluoroacetic acid R* and dilute to 1000 mL with *acetonitrile R1*;

Time (min)	Flow rate (mL/min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	0.75	100	0
10 - 125	0.75	100 → 39	0 → 61
125 - 135	1.25	39 → 17	61 → 83

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Flow rate (mL/min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
135 - 145	1.25	17 → 0	83 → 100
145 - 150	1.25	100	0

Detection Spectrophotometer at 214 nm.

Equilibration At initial conditions for at least 15 min. Carry out a blank run using the above-mentioned gradient.

Injection 50 µL.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of erythropoietin digest supplied with *erythropoietin for physicochemical tests CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

TESTS

Protein (*2.5.33, Method I*)

80 per cent to 120 per cent of the stated concentration.

Test solution Dilute the preparation to be examined in a 4 g/L solution of *ammonium hydrogen carbonate R*.

Record the absorbance spectrum between 250 nm and 400 nm. Measure the value at the absorbance maximum (276-280 nm), after correction for any light scattering, measured up to 400 nm. Calculate the concentration of erythropoietin taking the specific absorbance to be 7.43.

Dimers and related substances with molecular masses greater than that of erythropoietin

Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution Dilute the preparation to be examined in the mobile phase to obtain a concentration of 0.2 mg/mL.

Resolution solution Dissolve the contents of a vial of *erythropoietin for SEC system suitability CRS* in the mobile phase to obtain a concentration of 0.2 mg/mL.

Reference solution Dilute 20 µL of the resolution solution to 1.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5 µm), of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 20 000 to 200 000.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Dissolve 1.15 g of *anhydrous disodium hydrogen phosphate R*, 0.2 g of *potassium dihydrogen phosphate R* and 23.4 g of *sodium chloride R* in 900 mL of *water for chromatography R*, adjust to pH 7.4 if necessary, and dilute to 1000 mL with *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 100 µL.

Run time Twice the retention time of erythropoietin monomer.

Relative retention With reference to erythropoietin monomer: erythropoietin dimer = about 0.9.

System suitability:

— the area of the principal peak in the chromatogram obtained with the reference solution is 1.5 per cent to 2.5 per cent of the area of the principal peak in the chromatogram obtained with the resolution solution;

— *resolution*: minimum 1.5 between the peaks due to erythropoietin dimer and erythropoietin monomer in the chromatogram obtained with the resolution solution.

Limit:

— *sum of the peaks eluted before the principal peak*: maximum 2.0 per cent; disregard any peak with a retention time greater than that of the principal peak.

Sialic acids

Minimum 10 mol of sialic acids (calculated as *N*-acetylneuraminic acid) per mole of erythropoietin.

Test solution (a) Dilute the preparation to be examined in the mobile phase used in the test for dimers and related substances with molecular masses greater than that of erythropoietin to obtain a concentration of 0.3 mg/mL.

Test solution (b) To 0.5 mL of test solution (a) add 0.5 mL of the mobile phase used in the test for dimers and related substances with molecular masses greater than that of erythropoietin.

Reference solution (a) Dissolve a suitable amount of *N-acetylneuraminic acid R* in *water R* to obtain a concentration of 0.1 mg/mL.

Reference solution (b) To 0.8 mL of reference solution (a) add 0.2 mL of *water R*.

Reference solution (c) To 0.6 mL of reference solution (a) add 0.4 mL of *water R*.

Reference solution (d) To 0.4 mL of reference solution (a) add 0.6 mL of *water R*.

Reference solution (e) To 0.2 mL of reference solution (a) add 0.8 mL of *water R*.

Reference solution (f) Use *water R*.

www.webofpharma.com

https://thuocngocanh.com/

Carry out the test in triplicate. Transfer 100 µL of each of the test and reference solutions to 10 mL glass test tubes. To each tube add 1.0 mL of *resorcinol reagent R*. Stopper the tubes and incubate at 100 °C for 30 min. Cool on ice. To each tube, add 2.0 mL of a mixture of 12 volumes of *butanol R* and 48 volumes of *butyl acetate R*. Mix vigorously, and allow the 2 phases to separate. Ensuring that the upper phase is completely clear, remove the upper phase, taking care to exclude completely any of the lower phase. Measure the absorbance (*2.2.25*) of all samples at 580 nm. Using the calibration curve generated by the reference solutions, determine the content of sialic acids in test solutions (a) and (b) and calculate the mean. Calculate the number of moles of sialic acids per mole of erythropoietin assuming that the relative molecular mass of erythropoietin is 30 600 and that the relative molecular mass of *N*-acetylneuraminic acid is 309.

System suitability:

— the individual replicates agree to within ± 10 per cent of each other;

— the value obtained from reference solution (a) is between 1.5 and 3.3 times that obtained with test solution (a).

Bacterial endotoxins (*2.6.14*)

Less than 20 IU in the volume that contains 100 000 IU of erythropoietin.

ASSAY

The activity of the preparation is compared with that of *erythropoietin BRP* and expressed in International Units (IU).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits of the estimated potency (P = 0.95) are not less than 64 per cent and not more than 156 per cent of the stated potency.

Carry out the determination of potency by Method A or B.

A. In polycythaemic mice

The activity of the preparation is estimated by examining, under given conditions, its effect in stimulating the incorporation of ^{59}Fe into circulating red blood cells of mice made polycythaemic by exposure to reduced atmospheric pressure.

The following schedule, using treatment in a hypobaric chamber, has been found to be suitable.

Induce polycythaemia in female mice of the same strain, weighing 16-18 g. Place the mice in a hypoxic chamber and reduce the pressure to 0.6 atmospheres. After 3 days at 0.6 atmospheres, further reduce the pressure to 0.4-0.5 atmospheres and maintain the animals at this pressure for a further 11 days (the partial vacuum is interrupted daily for a maximum of 1 h at about 11:00 a.m., in order to clean the cages and feed the animals). At the end of the specified period, return the mice to normal atmospheric conditions. Randomly distribute the mice into cages, each containing 6 animals, and mark them.

Test solution (a) Dilute the substance to be examined in *phosphate-albumin buffered saline pH 7.2 R1* to obtain a concentration of 0.2 IU/mL.

Test solution (b) Mix equal volumes of test solution (a) and *phosphate-albumin buffered saline pH 7.2 R1*.

Test solution (c) Mix equal volumes of test solution (b) and *phosphate-albumin buffered saline pH 7.2 R1*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve *erythropoietin BRP* in *phosphate-albumin buffered saline pH 7.2 R1* to obtain a concentration of 0.2 IU/mL.

Reference solution (b) Mix equal volumes of reference solution (a) and *phosphate-albumin buffered saline pH 7.2 R1*.

Reference solution (c) Mix equal volumes of reference solution (b) and *phosphate-albumin buffered saline pH 7.2 R1*.

Radiolabelled ferric [^{59}Fe] chloride solution, concentrated Use a commercially available solution of [^{59}Fe]ferric chloride (approximate specific activity: 100-1000 MBq/mg of Fe).

Radiolabelled [^{59}Fe]ferric chloride solution Dilute the concentrated radiolabelled [^{59}Fe]ferric chloride solution in *Sodium citrate buffer solution pH 7.8 (0.034 M sodium citrate, 0.101 M sodium chloride) R* to obtain a solution with an activity of 3.7×10^4 Bq/mL.

The concentrations of the test solutions and reference solutions may need to be modified, based on the response range of the animals used.

3 days after returning the animals to atmospheric pressure, inject each animal subcutaneously with 0.2 mL of one of the solutions. The 6 animals in each cage must each receive one of the 6 different treatments (3 test solutions and 3 reference solutions), and the order of injection must be separately randomised for each cage. A minimum of 8 cages is recommended. 2 days after injection of the test or reference solution, inject each animal intraperitoneally with 0.2 mL of radiolabelled [^{59}Fe]ferric chloride solution. The order of the injections must be the same as that of the erythropoietin injections, and the time interval between administration of the erythropoietin and the radiolabelled ferric chloride solution must be the same for each animal. After a further 48 h, anaesthetise each animal by injection of a suitable anaesthetic, record body weights and withdraw blood samples (0.65 mL) into haematocrit capillaries from the bifurcation of the aorta. After determining the packed cell volume for each sample, measure the radioactivity.

Calculate the response (percentage of iron-59 in total circulating blood) for each mouse using the expression:

$$\frac{A_s \times M \times 7.5}{A_t \times V_s}$$

A_s = radioactivity in the sample;

A_t = total radioactivity injected;

7.5 = total blood volume as per cent body weight;

M = body weight, in grams;

V_s = sample volume.

Calculate the potency by the usual statistical methods for a parallel line assay. Eliminate from the calculation any animal where the packed cell volume is less than 54 per cent, or where the body weight is more than 24 g.

B. In normocythaemic mice

The assay is based on the measurement of stimulation of reticulocyte production in normocythaemic mice.

www.webofpharma.com

https://thuocngocanh.com/

The assay may be carried out using the following procedure:

Test solution (a) Dilute the preparation to be examined in *phosphate-albumin buffered saline pH 7.2 R1* to obtain a concentration of 80 IU/mL.

Test solution (b) Mix equal volumes of test solution (a) and *phosphate-albumin buffered saline pH 7.2 R1*.

Test solution (c) Mix equal volumes of test solution (b) and *phosphate-albumin buffered saline pH 7.2 R1*.

Reference solution (a) Dissolve *erythropoietin BRP* in *phosphate-albumin buffered saline pH 7.2 R1* to obtain a concentration of 80 IU/mL.

Reference solution (b) Mix equal volumes of reference solution (a) and *phosphate-albumin buffered saline pH 7.2 R1*.

Reference solution (c) Mix equal volumes of reference solution (b) and *phosphate-albumin buffered saline pH 7.2 R1*.

The exact concentrations of the test solutions and reference solutions may need to be modified, based on the response range of the animals used.

At the beginning of the assay procedure, randomly distribute mice of a suitable age and strain (8-week old B6D2F1 mice are suitable) into 6 cages. A minimum of 8 mice per cage is recommended. Inject each animal subcutaneously with 0.5 mL of the appropriate treatment (one solution per cage) and put the animal in a new cage. Combine the mice in such a way that each cage housing the treated mice contains one mouse out of the 6 different treatments (3 test solutions and 3 reference solutions, 6 mice per cage). 4 days after the injections, collect blood samples from the animals and determine the number of reticulocytes using a suitable procedure.

The following method may be employed:

The volume of blood, dilution procedure and fluorescent reagent may need to be modified to ensure maximum development and stability of fluorescence.

Colorant solution, concentrated Use a solution of thiazole orange suitable for the determination of reticulocytes. Prepare at a concentration twice that necessary for the analysis.

Proceed with the following dilution steps. Dilute whole blood 500-fold in the buffer used to prepare the colorant solution. Dilute this solution 2-fold in the concentrated colorant solution. After staining for 3-10 min, determine the reticulocyte count microfluorometrically in a flow cytometer. The percentage of reticulocytes is determined using a biparametric histogram: number of cells/red fluorescence (620 nm).

Calculate the potency by the usual statistical methods for a parallel line assay.

STORAGE

In an airtight container at a temperature below -20 °C. Avoid repeated freezing and thawing.

LABELLING

The label states:

www.webofpharma.com

https://thuvienthuocngocanh.com/

— the erythropoietin content in milligrams per millilitre;

— the activity in International Units per millilitre;

— the name and the concentration of any other excipients.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythropoietin Injection

General Notices

Action and use

Erythropoietin analogue.

DEFINITION

Erythropoietin Injection is a sterile solution of Erythropoietin Concentrated Solution in a suitable liquid. It is supplied as a ready-to-use solution.

PRODUCTION

The test for 'Dimers and substances of higher molecular weight' does not apply to those products containing human serum albumin that have been validated to show aggregation does not occur.

The injection complies with the requirements stated under Parenteral Preparations and, when supplied as a ready-to-use solution, with the following requirements.

Potency

The estimated potency is not less than 80% and not more than 125% of the stated potency.

CHARACTERISTICS

A clear, colourless solution virtually free from particles.

IDENTIFICATION

A. The result calculated under Assay complies with the specification stated under Potency.

B. Carry out the method for polyacrylamide gel electrophoresis, Appendix III F, using slab gels 0.75 mm thick and about 16 cm square (or 7 cm × 8 cm) and 12% *acrylamide* as the resolving gel and the following solutions:

(1) Concentrate or dilute, if necessary, the injection being examined to give a solution containing 2000 IU per mL in *water;* and then add 1 volume of SDS-PAGE sample buffer (concentrated).

(2) Dissolve the contents of a vial of *erythropoietin for physiochemical tests EPCRS* in water to obtain a 0.0017% solution and then add 1 volume of SDS-PAGE sample buffer (concentrated).

(3) A solution of pre-stained molecular weight markers suitable for calibrating SDS-polyacrylamide gels in the range of 10 to 70 kDa and suitable for the electrotransfer to an appropriate membrane.

Boil solutions (1), (2) and (3) for 2 minutes. Apply 20 µL (or 15 µL for 7 cm × 8 cm slab gels) of the solutions separately to the surface of the gel in the following order: solution (2), solution (1), solution (3). At the end of the separation, remove the gel-cassette from the apparatus.

www.webofpharma.com

https://thuocngocanh.com/

Immunoblotting is carried out as follows. Transfer the gel onto a membrane suitable for the immobilisation of proteins, using commercially available electrotransfer equipment and following the manufacturer's instructions. After electrotransfer, incubate the membrane in a neutral isotonic buffer containing a suitable blocking agent (for example, 50 g per litre of dried milk or 10% v/v foetal calf serum), for 1 to 2 hours, followed by incubation for 1 to 14 hours in the same blocking solution with a suitable dilution of either a polyclonal or monoclonal anti-erythropoietin antibody. Detect erythropoietin-bound antibody using a suitable enzyme or radiolabelled antibody (for example, an alkaline phosphatase-conjugated second antibody). The precise details of blocking agents, concentrations and incubation times should be optimised using the principles set out in *Immunochemical methods*, Appendix XIV B.

SYSTEM SUITABILITY

The test is not valid unless, in the electrophoretogram obtained with solution (3), the molecular weight markers are resolved on the membrane into discrete bands, with a linear relationship between distance migrated and logarithm_{10} of the molecular weight.

CONFIRMATION

The electrophoretogram obtained with solution (1) shows a single broad band corresponding in position and intensity to the single band seen in the electrophoretogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.6 to 7.4, Appendix V L.

Dimers and related substances of higher molecular weight

Use method A or method B.

A. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions and the *normalisation* procedure.

(1) Dilute the injection, if necessary, with the mobile phase to give a solution containing 1,000 IU of Erythropoietin per mL.

(2) Dissolve the contents of a vial of *erythropoietin for SEC system suitability EPCRS* in the mobile phase to obtain a 0.0005% w/v solution.

(3) Dilute 1 volume of solution (2) to 50 volumes with mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 7.5 mm) packed with *hydrophilic silica gel for chromatography* (5 µm) of a grade suitable for fractionation of globular proteins in the molecular weight range of 20,000 to 200,000 (TSK G3000SWXL is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use fluorimetric detection with an excitation wavelength of 280 nm and an emission wavelength of 340 nm.

(f) Inject 100 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of erythropoietin monomer.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

0.115% w/v of *anhydrous disodium hydrogen orthophosphate*, 0.02% w/v of *potassium dihydrogen orthophosphate* and 2.34% w/v of *sodium chloride* in *water;* if necessary, adjust to pH 7.3.

SYSTEM SUITABILITY

The test is not valid unless:

When the chromatograms are recorded under the prescribed conditions, the retention time of the peak due to erythropoietin dimer is about 25 minutes, and the retention time of the peak due to erythropoietin monomer is about 28 minutes.

in the chromatogram obtained with solution (2) aggregates are present;

in the chromatogram obtained with solution (2) the *resolution* between the peaks due to erythropoietin dimer and erythropoietin monomer is at least 0.8 and the relative standard deviation of erythromycin monomer is less than 10%

LIMITS

In the chromatogram obtained with solution (1) the total area of any peaks eluting before the principal peak is not greater than 2.0%.

In the chromatogram obtained with solution (3) the area of the principal peak is 1.5 to 2.5% of the area of the principal peak in the chromatogram obtained with the solution (1).

B. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions prepared in solution C.

Solution A 2.28% w/v Dipotassium Hydrogen Phosphate Trihydrate and 1.49% w/v *potassium chloride,* adjusted to pH 6.8 with 85% w/w *orthophosphoric acid*.

Solution B 0.43% w/v *sodium chloride*, 0.103% w/v *sodium dihydrogen orthophosphate monohydrate*, 0.223% w/v *disodium hydrogen orthophosphate dihydrate*, 0.5% w/v *glycine* and 0.03% w/v *polysorbate 80,* adjusted to pH 6.9.

Solution C 2 volumes of solution A and 1 volume of solution B

(1) Prepare the injection being examined as given in the Table below using the following solutions.
(2) Dissolve the contents of a vial of *erythropoietin for SEC system suitability EPCRS* in the sample dilution buffer to obtain a 0.001% w/v solution.
(3) Dilute 0.02 mL of solution (1) to 1 mL with solution C.

Sample solution IU per mL	µg per mL	Dilution	Diluent	Final concentration of polysorbate 80 w/v	Injection volume µL
2,000	16.67	Undiluted	Not applicable	0.03%	50
4,000	33.33	Undiluted	Not applicable	0.03%	50
10,000	83.33	1:3	Solution A	0.01%	100
40,000	333.33	1:6	Solution C	0.01%	50

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (30 cm × 7.8 mm) packed with *hydrophilic silica gel for chromatography* of a grade suitable for fractionation of globular proteins in the molecular weight range of 20,000 to 200,000 (TSK G 3000 SWxl is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.3 mL per minute.

(d) Use an ambient column temperature.

(e) Use fluorimetric detection with an excitation wavelength of 280 nm and an emission wavelength of 345 nm.

(f) For solution (2) use an injection volume of 50 µL. For solutions (1) and (3) use injection volumes as stated in the sample preparation table.

(g) Allow the chromatography to proceed for twice the retention time of erythropoietin monomer.

MOBILE PHASE

25 volumes of *propan-2-ol*, 75 volumes of solution A

SYSTEM SUITABILITY

The test is not valid unless:

When the chromatograms are recorded under the prescribed conditions, the retention time of the peak due to erythropoietin dimer is about 25 minutes, and the retention time of the peak due to erythropoietin monomer is about 28 minutes

solution B shows no interfering peaks;

in the chromatogram obtained with solution (2) the *resolution* between the peaks due to erythropoietin dimer and erythropoietin monomer is at least 0.8 and the relative standard deviation of erythromycin monomer is less than 10%

LIMITS

In the chromatogram obtained with solution (1) the total area of any peaks eluting before the principal peak is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (2.0%).

The retention time of the principal peak is about 30 minutes.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 20 IU in a volume containing 10,000 IU of Erythropoietin.

ASSAY

Carry out the Assay using method A or method B.

The activity of the preparation is compared with that of *erythropoietin EPBRP* and expressed in International Units (IU).

The confidence limits of the estimated potency (P = 0.95) are not less than 64% and not more than 156% of the stated potency.

A. In polycythaemic mice

www.webofpharma.com

https://thuocngocanh.com/

The activity of the preparation is estimated by examining, under given conditions, its effect in stimulating the incorporation of ^{59}Fe into circulating red blood cells of mice made polycythaemic by exposure to reduced atmospheric pressure.

The following schedule, using treatment in a hypobaric chamber, has been found to be suitable.

Induce polycythaemia in female mice of the same strain, weighing 16 to 18 g. Place the mice in a hypoxic chamber and reduce the pressure to 0.6 atmospheres. After 3 days at 0.6 atmospheres, further reduce the pressure to between 0.4 and 0.5 atmospheres and maintain the animals at this pressure for a further 11 days (the partial vacuum is interrupted daily for a maximum of 1 hour at about 11:00 a.m., in order to clean the cages and feed the animals). At the end of the specified period, return the mice to normal atmospheric conditions. Randomly distribute the mice into cages, each containing 6 animals, and mark them. Use the following solutions:

(1) Dilute the substance to be examined in *phosphate-albumin buffered saline pH 7.2 R1* to obtain a concentration of 0.2 IU per mL.
(2) Mix equal volumes of solution (1) and *phosphate-albumin buffered saline pH 7.2 R1*
(3) Mix equal volumes of solution (2) and *phosphate-albumin buffered saline pH 7.2 R1*
(4) Dissolve *erythropoietin EPBRP* in *phosphate-albumin buffered saline pH 7.2 R1*
(5) Mix equal volumes of solution (4) and *phosphate-albumin buffered saline pH 7.2 R1*
(6) Mix equal volumes of solution (5) and *phosphate-albumin buffered saline pH 7.2 R1*
(7) Use a commercially available solution of [^{59}Fe] ferric chloride (approximate specific activity: 100 to 1000 MBq per mg of Fe).

Radiolabelled [^{59}Fe] ferric chloride solution Dilute the concentrated radiolabelled [^{59}Fe] ferric chloride solution in *sodium citrate buffer solution pH 7.8* to obtain a solution with an activity of 3.7×10^4 Bq per mL.

The concentrations of the test solutions and reference solutions may need to be modified, based on the response range of the animals used.

Three days after returning the animals to atmospheric pressure, inject each animal subcutaneously with 0.2 mL of one of the solutions. The 6 animals in each cage must each receive one of the 6 different treatments (solutions 1 to 6); the order of injection must be separately randomised for each cage. A minimum of 8 cages is recommended. Two days after injection of solutions 1 to 6, inject each animal intraperitoneally with 0.2 mL of solution 7. The order of the injections must be the same as that of the erythropoietin injections, and the time interval between administration of the erythropoietin and the radiolabelled ferric chloride solution must be the same for each animal. After a further 48 hours, anaesthetise each animal by injection of a suitable anaesthetic, record body weights and withdraw blood samples (0.65 mL) into haematocrit capillaries from the bifurcation of the aorta. After determining the packed cell volume for each sample, measure the radioactivity.

Calculate the response (percentage of ^{59}Fe in total circulating blood) for each mouse using the expression:

$$\frac{A_s \times M \times 7.5}{A_t \times V_s}$$

A_s = radioactivity in the sample,

A_t = total radioactivity injected,

www.webofpharma.com

https://thuocngocanh.com/

7.5	=	total blood volume as per cent body weight,
M	=	body weight, in grams,
V_s	=	sample volume.

Calculate the potency by the usual statistical methods for a parallel line assay. Eliminate from the calculation any animal where the packed cell volume is less than 54%, or where the body weight is more than 24 g.

B. In normocythaemic mice

The Assay is based on the measurement of stimulation of reticulocyte production in normocythaemic mice.

The Assay may be carried out using the following solutions:

(1) Dilute the preparation being examined in *phosphate-albumin buffered saline pH 7.2 R1* to obtain a concentration of 80 IU per mL.
(2) Mix equal volumes of solution (1) and *phosphate-albumin buffered saline pH 7.2 R1*
(3) Mix equal volumes of solution (2) and *phosphate-albumin buffered saline pH 7.2 R1*.
(4) Dissolve *erythropoietin EPBRP* in *phosphate-albumin buffered saline pH 7.2 R1* to obtain a concentration of 80 IU per mL.
(5) Mix equal volumes of solution (4) and *phosphate-albumin buffered saline pH 7.2 R1*.
(6) Mix equal volumes of solution (5) and *phosphate-albumin buffered saline pH 7.2 R1*.

The exact concentrations of the test solutions and reference solutions may need to be modified, based on the response range of the animals used.

At the beginning of the assay procedure, randomly distribute mice of a suitable age and strain (8-week old B6D2F1 mice are suitable) into 6 cages. A minimum of 8 mice per cage is recommended. Inject each animal subcutaneously with 0.5 mL of the appropriate treatment (one solution per cage) and put the animal in a new cage. Combine the mice in such a way that each cage housing the treated mice contains one mouse out of the 6 different treatments (solutions 1 to 6, 6 mice per cage). 4 days after the injections, collect blood samples from the animals and determine the number of reticulocytes using a suitable procedure.

The following method may be employed:

The volume of blood, dilution procedure and fluorescent reagent may need to be modified to ensure maximum development and stability of fluorescence.

Colorant solution, concentrated Use a solution of thiazole orange suitable for the determination of reticulocytes. Prepare at a concentration twice that necessary for the analysis.

Proceed with the following dilution steps. Dilute whole blood 500-fold in the buffer used to prepare the colorant solution. Dilute this solution 2-fold in the concentrated colorant solution. After staining for 3 to 10 minutes, determine the reticulocyte count microfluorometrically in a flow cytometer. The percentage of reticulocytes is determined using a biparametric histogram: number of cells/red fluorescence (620 nm).

Calculate the potency by the usual statistical methods for a parallel line assay.

STORAGE

www.webofpharma.com

https://thietbiuocngocanh.com/

When supplied as a ready-to-use solution, Erythropoietin Injection should be stored protected from light at a temperature of 2° to 8°.

Erythropoietin Injection prepared by dissolving the contents of a sealed container in the liquid stated on the label should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

LABELLING

The label states the number of IU (Units) in a suitable dose-volume.

ERYTHROPOIETIN FOR INJECTION

DEFINITION

Erythropoietin for Injection is a freeze-dried, sterile preparation prepared from Erythropoietin Concentrated Solution. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

IDENTIFICATION

A. It gives the appropriate response when examined using the conditions under Assay.

B. Comply with Identification test B as described for the ready to use solution. Prepare solution (1) by dissolving a quantity of powder in *water* to contain 2000 IU per mL. Prepare solution (2) by dissolving the contents of a vial of *erythropoietin for SEC system suitability EPCRS* in *water* to obtain a 0.0017% w/v solution. Add 1 volume of *SDS-PAGE sample buffer (concentrated)* to each solution.

TESTS

Dimers and related substances of higher molecular weight

Comply with the tests A or B described for the ready to use solution using the following test solution.

(1) Dissolve a quantity of the powder in the mobile phase to give a solution containing 1,000 IU of erythropoietin per mL.

Water

Not more than 4.0% w/w, Appendix IX C, Method 1.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. The endotoxin limit concentration is less than 20 IU in a volume containing 10,000 IU of Erythropoietin.

ASSAY

Carry out the Assay as described for the ready to use solution using the following solutions:

www.webofpharma.com

https://thuocngocanh.com/

A. In polycythaemic mice

(1) 0.2 IU per mL in *phosphate-albumin buffered saline pH 7.2 R1*.

B. In normocythaemic mice

(1) 80 IU per mL in *phosphate-albumin buffered saline pH 7.2 R1*

LABELLING

The label of the sealed container states the number of IU (Units) contained in it.

© Crown Copyright 2022

www.webofpharma.com

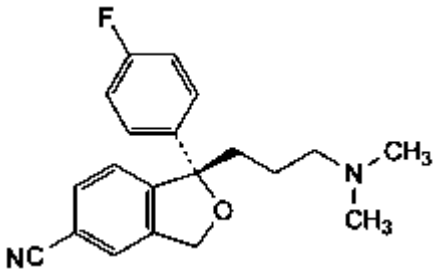
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Escitalopram

General Notices

(Ph. Eur. monograph 2758)



$C_{20}H_{21}FN_2O$ 324.4 *128196-01-0*

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

Ph Eur

DEFINITION

(1*S*)-1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in anhydrous ethanol and in toluene.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *escitalopram CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Enantiomeric purity (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 3.4 g of potassium dihydrogen phosphate R in 900 mL of water R; adjust to pH 3.0 with phosphoric acid R and dilute to 1000 mL with water R.

Test solution Dissolve 25 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of escitalopram for system suitability CRS (containing impurity D) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, buffer solution (10:90 *V/V*);

— *mobile phase B*: buffer solution, acetonitrile R (35:65 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 2	95	5	1.0
2 - 37	95 → 65	5 → 35	1.0
37 - 47	65 → 0	35 → 100	1.0
47 - 62	0	100	2.0

Detection Spectrophotometer at 237 nm and at 254 nm.

Injection 20 µL.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *escitalopram for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to escitalopram (retention time = about 38 min): impurity D = about 0.98.

System suitability Reference solution (a) at 237 nm:

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to escitalopram.

Calculation of percentage contents:

— for each impurity, use the concentration of escitalopram in reference solution (b) at 237 nm.

Limits:

— *unspecified impurities at 237 nm and at 254 nm*: for each impurity, maximum 0.10 per cent;

— *total at 237 nm*: maximum 0.5 per cent;

— *reporting threshold at 237 nm*: 0.05 per cent.

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *citalopram hydrobromide CRS* (containing equal amounts of impurity K and escitalopram) in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *protein derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, *0.05 M phosphate buffer solution pH 7.0 R* (15:85 *V/V*).

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 240 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 15 µL.

Run time Twice the retention time of escitalopram.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity K.

Relative retention With reference to escitalopram (retention time = about 11 min): impurity K = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 1.3 between the peaks due to escitalopram and impurity K;

— *symmetry factor*: maximum 4.0 for the peak due to escitalopram; maximum 4.0 for the peak due to impurity K.

Limits:

— *impurity K*: maximum 2.0 per cent;

— *reporting threshold*: 0.10 per cent (reference solution (b)).

Water (2.5.12)

Maximum 0.2 per cent, determined on 0.500 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *acetic anhydride R* and 75 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 32.44 mg of $C_{20}H_{21}FN_2O$.

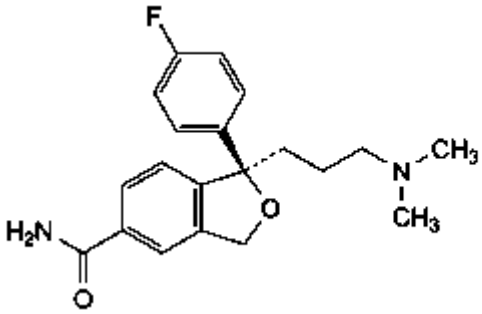
IMPURITIES

Specified impurities *K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H, I, J, L, M.*

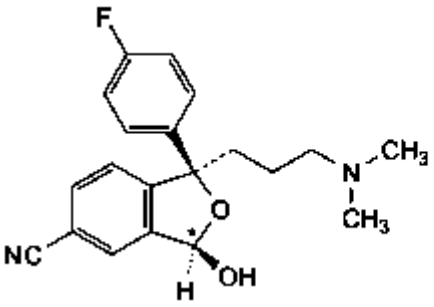
www.webofpharma.com

https://thuocngocanh.com/



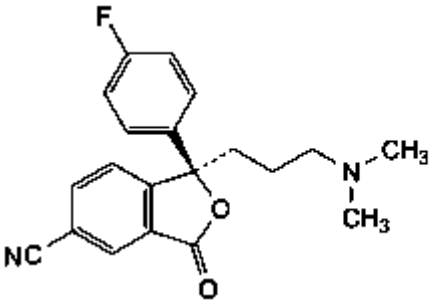
and enantiomer

A. (1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carboxamide,



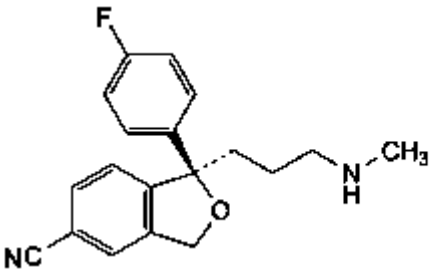
its epimer at C* and their enantiomers

B. mixture of (1*RS*,3*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydro-2-benzofuran-5-carbonitrile and (1*RS*,3*SR*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydro-2-benzofuran-5-carbonitrile,



and enantiomer

C. (1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-oxo-1,3-dihydro-2-benzofuran-5-carbonitrile,

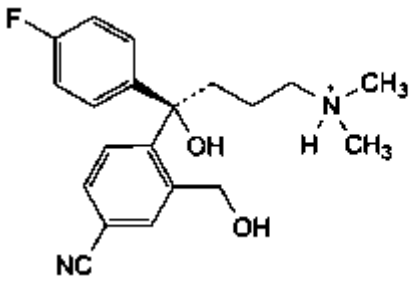


and enantiomer

D. (1*RS*)-1-(4-fluorophenyl)-1-[3-(methylamino)propyl]-1,3-dihydro-2-benzofuran-5-carbonitrile,

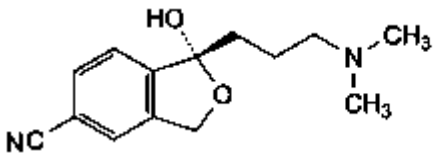
www.webofpharma.com

https://thuocngocanh.com/



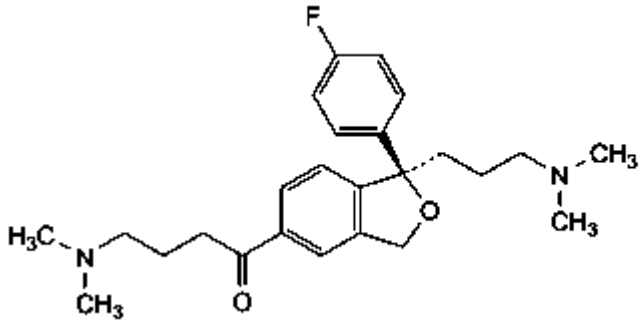
and enantiomer

E. (4*RS*)-4-[4-cyano-2-(hydroxymethyl)phenyl]-4-(4-fluorophenyl)-4-hydroxy-*N*,*N*-dimethylbutan-1-aminium,



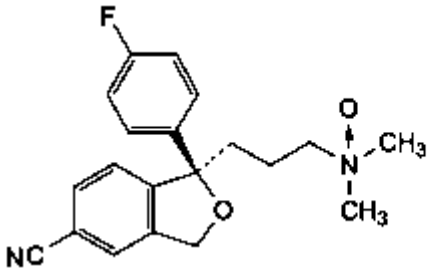
and enantiomer

F. (1*RS*)-1-[3-(dimethylamino)propyl]-1-hydroxy-1,3-dihydro-2-benzofuran-5-carbonitrile,



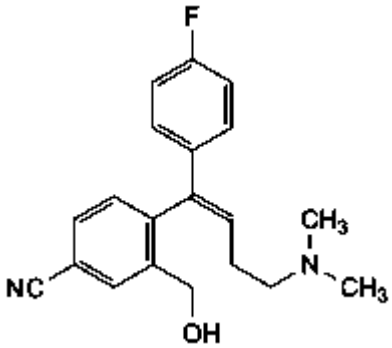
and enantiomer

G. 4-(dimethylamino)-1-[(1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-yl]butan-1-one,



and enantiomer

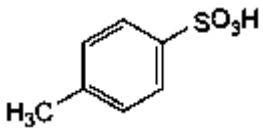
H. 3-[(1*RS*)-5-cyano-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-1-yl]-*N*,*N*-dimethylpropan-1-amine *N*-oxide,



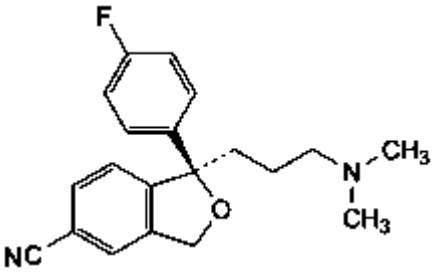
www.webofpharma.com

https://thuocngocanh.com/

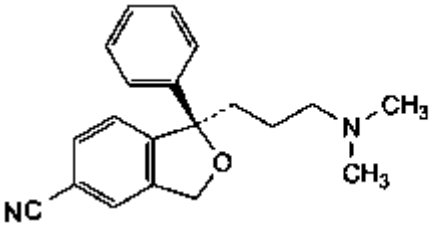
I. 4-[(1*Z*)-4-(dimethylamino)-1-(4-fluorophenyl)but-1-en-1-yl]-3-(hydroxymethyl)benzonitrile,



J. 4-methylbenzenesulfonic acid (*p*-toluenesulfonic acid),

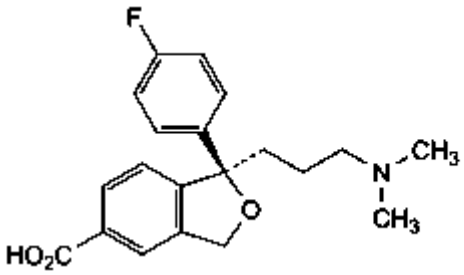


K. (1*R*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile,



and enantiomer

L. (1*RS*)-1-[3-(dimethylamino)propyl]-1-phenyl-1,3-dihydro-2-benzofuran-5-carbonitrile,



and enantiomer

M. (1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carboxylic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

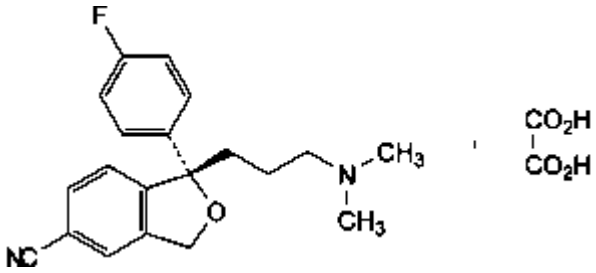
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Escitalopram Oxalate

General Notices

(Ph. Eur. monograph 2733)



$C_{22}H_{23}FN_2O_5$ 414.4 *219861-08-2*

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

Ph Eur

DEFINITION

(1*S*)-1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile hydrogen oxalate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in methanol, slightly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *escitalopram oxalate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Enantiomeric purity (see Tests).

TESTS

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 3.4 g of potassium dihydrogen phosphate R in 900 mL of water for chromatography R, adjust to pH 3.0 with phosphoric acid R and dilute to 1000 mL with water for chromatography R.

Test solution Dissolve 25 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 5 mg of escitalopram for system suitability CRS (containing impurity D) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, buffer solution (10:90 *V/V*);

— *mobile phase B*: buffer solution, acetonitrile R (35:65 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 2	95	5	1.0
2 - 37	95 → 65	5 → 35	1.0
37 - 47	65 → 0	35 → 100	1.0
47 - 62	0	100	2.0

Detection Spectrophotometer at 237 nm and at 254 nm.

Injection 20 µL.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *escitalopram for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to escitalopram (retention time = about 38 min): impurity D = about 0.98.

System suitability Reference solution (a) at 237 nm:

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to escitalopram.

Calculation of percentage contents:

— for each impurity, use the concentration of escitalopram oxalate in reference solution (b) at 237 nm.

Limits:

— *unspecified impurities at 237 nm and at 254 nm*: for each impurity, maximum 0.10 per cent;

— *total at 237 nm*: maximum 0.5 per cent;

— *reporting threshold at 237 nm*: 0.05 per cent.

Enantiomeric purity

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *citalopram hydrobromide CRS* (containing equal amounts of impurity K and escitalopram) in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *protein derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *acetonitrile R*, *0.05 M phosphate buffer solution pH 7.0 R* (15:85 *V/V*).

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 240 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 15 µL.

Run time Twice the retention time of escitalopram.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity K.

Relative retention With reference to escitalopram (retention time = about 11 min): impurity K = about 1.2.

System suitability Reference solution (a):

— *resolution*: minimum 1.3 between the peaks due to escitalopram and impurity K;

— *symmetry factor*: maximum 4.0 for the peak due to escitalopram; maximum 4.0 for the peak due to impurity K.

Limits:

— *impurity K*: maximum 2.0 per cent;

— *reporting threshold*: 0.10 per cent (reference solution (b)).

Water (2.5.12)

Maximum 1.0 per cent, determined on 0.250 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in a mixture of 5.0 mL of *acetic anhydride R* and 75 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 41.44 mg of $C_{22}H_{23}FN_2O_5$.

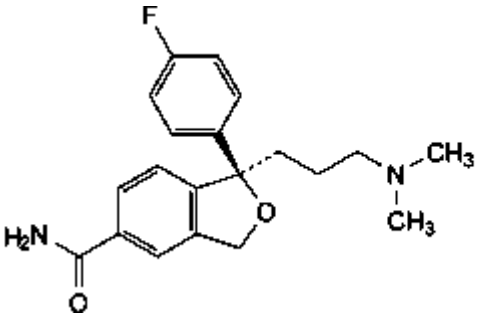
IMPURITIES

Specified impurities *K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H, I, J, L, M.*

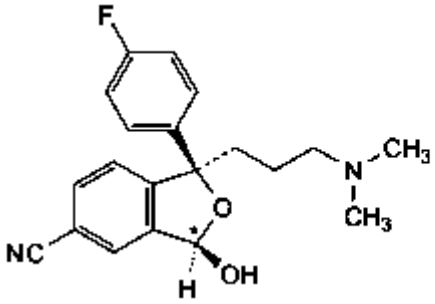
www.webofpharma.com

https://thuocngocanh.com/



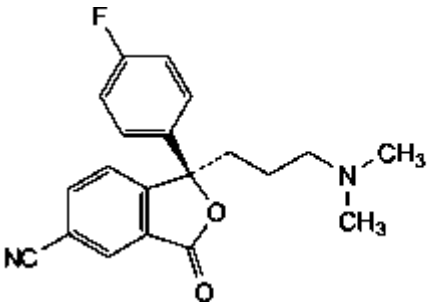
and enantiomer

A. (1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carboxamide,



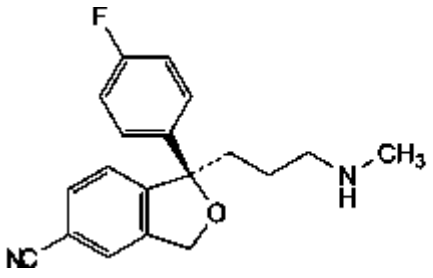
its epimer at C*
and their enantiomers

B. mixture of (1*RS*,3*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydro-2-benzofuran-5-carbonitrile and (1*RS*,3*SR*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydro-2-benzofuran-5-carbonitrile,



and enantiomer

C. (1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-oxo-1,3-dihydro-2-benzofuran-5-carbonitrile,

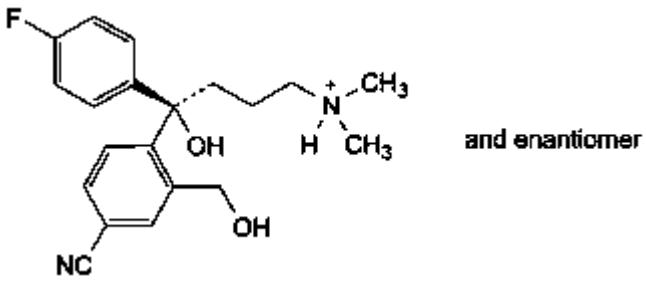


and enantiomer

D. (1*RS*)-1-(4-fluorophenyl)-1-[3-(methylamino)propyl]-1,3-dihydro-2-benzofuran-5-carbonitrile,

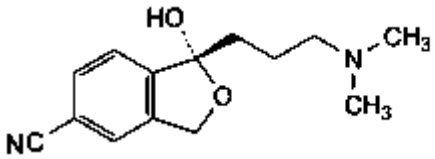
www.webofpharma.com

https://thuocngocanh.com/



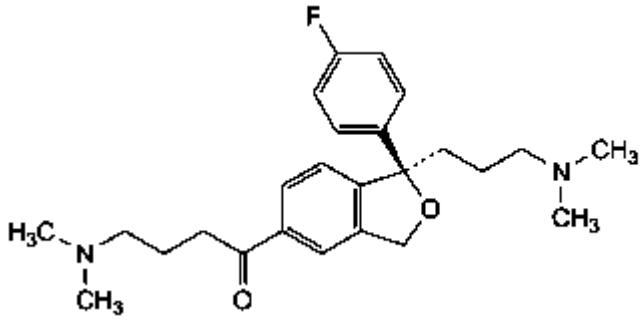
and enantiomer

E. (4*RS*)-4-[4-cyano-2-(hydroxymethyl)phenyl]-4-(4-fluorophenyl)-4-hydroxy-*N*,*N*-dimethylbutan-1-aminium,



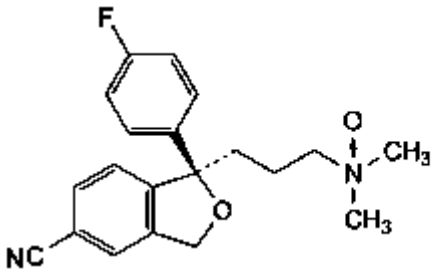
and enantiomer

F. (1*RS*)-1-[3-(dimethylamino)propyl]-1-hydroxy-1,3-dihydro-2-benzofuran-5-carbonitrile,



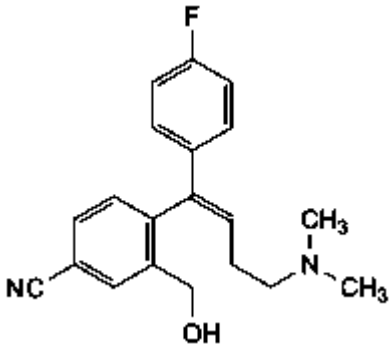
and enantiomer

G. 4-(dimethylamino)-1-[(1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-yl]butan-1-one,



and enantiomer

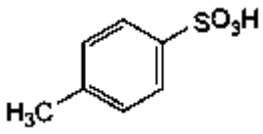
H. 3-[(1*RS*)-5-cyano-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-1-yl]-*N*,*N*-dimethylpropan-1-amine *N*-oxide,



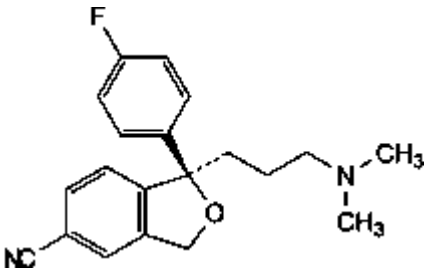
www.webofpharma.com

https://thuocngocanh.com/

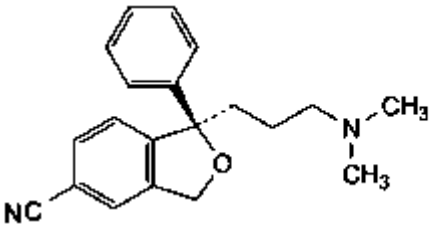
I. 4-[(1*Z*)-4-(dimethylamino)-1-(4-fluorophenyl)but-1-en-1-yl]-3-(hydroxymethyl)benzonitrile,



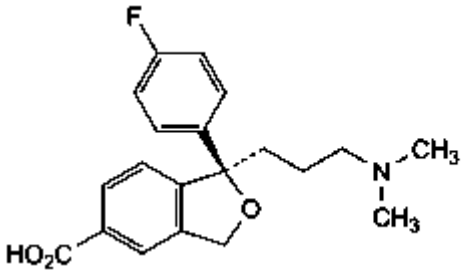
J. 4-methylbenzenesulfonic acid (*p*-toluenesulfonic acid),



K. (1*R*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile,


and enantiomer

L. (1*RS*)-1-[3-(dimethylamino)propyl]-1-phenyl-1,3-dihydro-2-benzofuran-5-carbonitrile,


and enantiomer

M. (1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carboxylic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

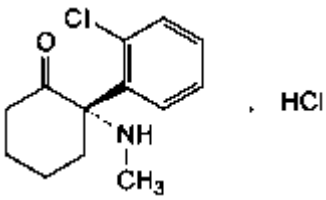
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Esketamine Hydrochloride

General Notices

(Ph. Eur. monograph 1742)



$C_{13}H_{17}Cl_2NO$ 274.2 *33643-47-9*

Action and use

General anaesthetic.

Ph Eur

DEFINITION

(2*S*)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.

Content

99.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in methanol, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Specific optical rotation (2.2.7): + 85.0 to + 95.0.

Dilute 12.5 mL of solution S (see Tests) to 40.0 mL with *water R*.

B. Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *Ph. Eur. reference spectrum of esketamine hydrochloride*.

C. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 8.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

3.5 to 4.5.

Dilute 12.5 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Impurity D

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *esketamine impurity D CRS* in *water R*, add 20 mL of the test solution and dilute to 50 mL with *water R*. Dilute 10 mL of this solution to 100 mL with *water R*.

Reference solution (b) Dilute 5.0 mL of the test solution to 25.0 mL with *water R*. Dilute 5.0 mL of this solution to 50.0 mL with *water R*.

Reference solution (c) Dilute 2.5 mL of reference solution (b) to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Precolumn:

— *size*: *l* = 0.01 m, Ø = 3.0 mm;

— *stationary phase*: *silica gel AGP for chiral chromatography R* (5 µm);

— *temperature*: 30 °C.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel AGP for chiral chromatography R* (5 µm);

— *temperature*: 30 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 16 volumes of *methanol R* and 84 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 7.0 with *potassium hydroxide R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 20 min.

Relative retention With reference to esketamine (retention time = about 10 min): impurity D = about 1.3.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to esketamine and impurity D in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 3 for the principal peak in the chromatogram obtained with reference solution (c).

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *ketamine impurity A CRS* in the mobile phase (using ultrasound, if necessary) and dilute to 10 mL with the mobile phase. To 1 mL of the solution add 0.5 mL of the test solution and dilute to 100 mL with the mobile phase. Prepare immediately before use.

Reference solution (b) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 0.95 g of *sodium hexanesulfonate R* in 1000 mL of a mixture of 25 volumes of *acetonitrile R* and 75 volumes of *water R* and add 4 mL of *acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL.

Run time 10 times the retention time of esketamine.

Relative retention With reference to esketamine: impurity A = about 1.6; impurity B = about 3.3; impurity C = about 4.6.

System suitability Reference solution (a):

— *retention time*: esketamine = 3.0 min to 4.5 min;

— *resolution*: minimum 1.5 between the peaks due to impurity A and esketamine.

Limits:

— *impurities A, B, C*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *methanol R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 27.42 mg of $C_{13}H_{17}Cl_2NO$.

STORAGE

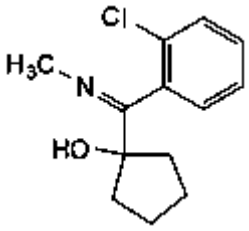
Protected from light.

IMPURITIES

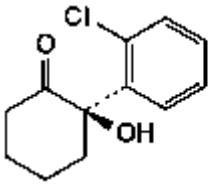
Specified impurities *A, B, C, D.*

www.webofpharma.com

https://thuocngocanh.com/

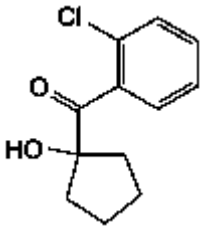


A. 1-[(2-chlorophenyl)(methylimino)methyl]cyclopentanol,

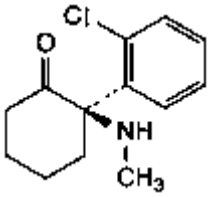


and enantiomer

B. (2*RS*)-2-(2-chlorophenyl)-2-hydroxycyclohexanone,



C. (2-chlorophenyl)(1-hydroxycyclopentyl)methanone,



D. (2*R*)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone ((*R*)-ketamine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Esomeprazole Gastro-resistant Capsules

General Notices

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Esomeprazole Gastro-resistant Capsules contain Esomeprazole Magnesium Dihydrate, Esomeprazole Magnesium Trihydrate or Esomeprazole Sodium. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of esomeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) Disperse a quantity of the capsule contents containing the equivalent of 40 mg of esomeprazole in 5 mL of *methanol*, dilute to 50 mL with solution A and filter (a 0.45-µm nylon filter is suitable). Further dilute 1 volume to 200 volumes with solution A.
(2) 0.0008% w/v of *omeprazole BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *α_1-acid-glycoprotein silica gel for chiral separation* (5 µm) (Chiralpak AGP is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 302 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

13 volumes of *acetonitrile* and 87 volumes of a solution containing 0.0025M *disodium hydrogen orthophosphate* and 0.005M *sodium dihydrogen orthophosphate*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to esomeprazole (retention time about 5 minutes) is: *(R)*-omeprazole (impurity F), about 0.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to *(R)*-omeprazole and esomeprazole is at least 3.0.

CONFIRMATION

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak due to esomeprazole in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to esomeprazole in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

Solution B 0.1 volumes of 10M *sodium hydroxide* and 10 volumes of *0.05M phosphate buffer solution pH 4.5*.

Solution C 5.2 volumes of 1M *anhydrous sodium dihydrogen orthophosphate* and 63.2 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate* and dilute to 1000 volumes with *water*. Adjust to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Use 700 mL of *0.05M phosphate buffer solution pH 4.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 60 minutes withdraw 5 mL of the medium and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the filtrate to 5 volumes with solution A and retain the samples for analysis. Proceed immediately to the final stage.
(2) 0.0002% w/v of *omeprazole BPCRS* in a mixture of 1 volume of solution A and 9 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (15 cm × 2 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable). Use a suitable guard column.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.25 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 302 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of solution C, 35 volumes of *water* and 40 volumes of *acetonitrile*, adjusted to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of omeprazole is about 4 minutes.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of esomeprazole released is not more than 10% of the stated amount.

Final stage (pH 6.8)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 1 minute of withdrawing the medium at completion of the first stage, add 200 mL of solution B, at a temperature of 37°, to the vessel.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter (a 0.45-µm nylon filter is suitable). To a volume of the filtrate expected to contain the equivalent of 0.05 mg of esomeprazole, add 1 volume of 0.25M *sodium hydroxide* and dilute to 25 volumes with solution A.

(2) 0.001% w/v of *omeprazole BPCRS* in a mixture of 1 volume of solution A and 9 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is between 0.8 and 2.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of $C_{17}H_{19}N_3O_3S$, in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of esomeprazole released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) To a quantity of the contents of the capsules containing the equivalent of 24 mg of esomeprazole, add 40 mL of *ethanol* and mix with the aid of ultrasound. Add 150 mL of solution A and further mix. Dilute with sufficient solution A to produce 250 mL and filter (a 0.45-µm nylon filter is suitable).

(2) Dilute 1 volume of solution (1) to 20 volumes with solution A. Dilute 1 volume of this solution to 10 volumes with *water*.

(3) 0.1% w/v of *omeprazole BPCRS* and 0.0005% w/v *omeprazole impurity D EPCRS*, each prepared by dissolving the reference material in 1 volume of *ethanol* and diluting to 5 volumes with solution A. Mix 1 volume of each solution and dilute to 10 volumes with *water*.

(4) Dilute 1 volume of solution (2) to 5 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil RP8 is suitable)

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 40 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of omeprazole.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of 0.14% w/v solution of *disodium hydrogen orthophosphate*, previously adjusted to pH 7.6 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to omeprazole (retention time about 8 minutes) are: impurity 1, about 0.25; impurity A, about 0.35; impurity E, about 0.4; impurity D, about 0.8; impurity 2, about 1.7 and impurity C, about 4.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) To a quantity of the contents of the capsules containing the equivalent of 24 mg of esomeprazole, add 40 mL of *ethanol* and mix with the aid of ultrasound. Add 150 mL of solution A and further mix. Dilute with sufficient solution A to produce 250 mL and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the resulting solution to 10 volumes with *water*.
(2) 0.0096% w/v of *omeprazole BPCRS* prepared by dissolving the reference material in 1 volume of *ethanol* and diluting to 5 volumes with solution A. Dilute 1 volume of the resulting solution to 10 volumes with *water*.
(3) 0.1% w/v of *omeprazole BPCRS* and 0.0005% w/v *omeprazole impurity D EPCRS*, each prepared by dissolving the reference material in 1 volume of *ethanol* and diluting to 5 volumes with solution A. Mix 1 volume of each solution and dilute to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a detection wavelength of 302 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is greater than 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_3O_3S$ in the capsules using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LABELLING

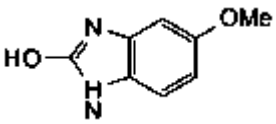
The quantity of active ingredient is stated in terms of the equivalent amount of esomeprazole.

IMPURITIES

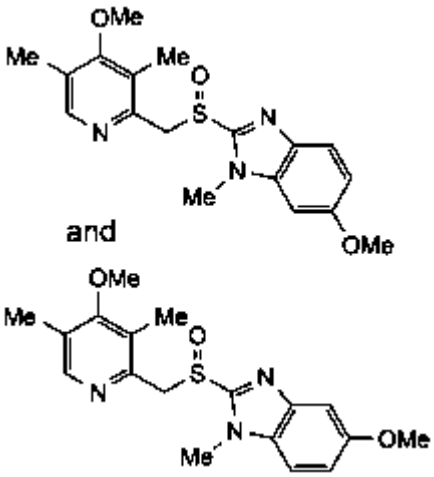
www.webofpharma.com

https://thuocngocanh.com/

The impurities limited by the requirements of this monograph include impurities A, C, D and E listed under Esomeprazole Magnesium Dihydrate and Esomeprazole Magnesium Trihydrate and:



1. 2-hydroxy-5-methoxybenzimidazole (5-methoxy-2-benzimidazolinone),



2. 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole, regioisomers.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Esomeprazole Gastro-resistant Granules

General Notices

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Esomeprazole Granules contain Esomeprazole Magnesium Trihydrate in a suitable basis. The granules are covered with a gastro-resistant coating.

The granules comply with the requirements stated under Granules and with the following requirements.

Content of esomeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) Shake a quantity of the granules containing the equivalent of 50 mg of esomeprazole in 100 mL of *water* and filter (a 0.2-mm mesh sieve is suitable). Rinse the granules on the sieve with 0.1mM *hydrochloric acid*. Disperse the granules in 100 mL of solution A, add 100 mL of *water* and dilute with *ethanol* to produce 250 mL and mix. To 1 volume, add 1 volume of *water*, dilute to 20 volumes with solution A and filter (a 0.45-µm PVDF filter is suitable).

(2) 0.001% w/v of *omeprazole BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *α_1-acid-glycoprotein silica gel for chiral separation* (5 µm) (Chiralpak AGP is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 302 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

13 volumes of *acetonitrile* and 87 volumes of a solution containing 0.0025M *disodium hydrogen orthophosphate* and 0.005M *sodium dihydrogen orthophosphate*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to esomeprazole (retention time about 5 minutes) is: *(R)*-omeprazole (impurity F), about 0.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to *(R)*-omeprazole and esomeprazole is at least 3.0.

CONFIRMATION

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak due to esomeprazole in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to esomeprazole in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

Solution B 0.1 volumes of 10M *sodium hydroxide* and 10 volumes of *0.05M phosphate buffer solution pH 4.5*.

Solution C 5.2 volumes of 1M *anhydrous sodium dihydrogen orthophosphate* and 63.2 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate* and dilute to 1000 volumes with *water*. Adjust to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Use 700 mL of *0.05M phosphate buffer solution pH 4.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 60 minutes withdraw 5 mL of the medium and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the filtrate to 5 volumes with solution A and retain the samples for analysis. Proceed immediately to the final stage.
(2) 0.0002% w/v of *omeprazole BPCRS* in a mixture of 1 volume of solution A and 9 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (15 cm × 2 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable). Use a suitable guard column.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.25 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 302 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of solution C, 35 volumes of *water* and 40 volumes of *acetonitrile*, adjusted to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of omeprazole is about 4 minutes.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of esomeprazole released is not more than 10% of the stated amount.

Final stage (pH 6.8)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 1 minute of withdrawing the medium at completion of the first stage, add 200 mL of solution B, at a temperature of 37°, to the vessel.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter (a 0.45-µm nylon filter is suitable). To a volume of the filtrate expected to contain the equivalent of 0.05 mg of esomeprazole, add 1 volume of 0.25M *sodium hydroxide* and dilute to 25 volumes with solution A.

(2) 0.001% w/v of *omeprazole BPCRS* in a mixture of 1 volume of solution A and 9 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is between 0.8 and 2.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of $C_{17}H_{19}N_3O_3S$, in the medium using the declared content of $C_{17}H_{19}N_3O_3S$, in *omeprazole BPCRS*.

LIMITS

The amount of esomeprazole released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) Shake a quantity of the granules containing the equivalent of 50 mg of esomeprazole in 100 mL of *water* and filter (a 0.2 mm mesh sieve is suitable). Rinse the granules on the sieve with 0.1mM *hydrochloric acid*. Disperse the granules in 100 mL of solution A, add 100 mL of *water* and dilute with *ethanol* to produce 250 mL and mix. Dilute 1 volume to 2 volumes with *water* and filter (a 0.45-µm PVDF filter is suitable).

(2) Dilute 1 volume of solution (1) to 20 volumes with solution A. Dilute 1 volume of this solution to 10 volumes with *water*.

(3) 0.0001% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*, prepared by dissolving the reference materials in 1 volume of *ethanol*, adding 2 volumes of solution A and diluting to 10 volumes with *water*.

(4) Dilute 1 volume of solution (2) to 5 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Microspher C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 302 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Solution D 5.2 volumes of 1.0M *sodium dihydrogen orthophosphate monohydrate*, 63 volumes of 0.5M *disodium hydrogen orthophosphate dihydrate* and dilute to 1000 volumes with *water*. Adjust to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

Mobile phase A 100 volumes of *acetonitrile*, 100 volumes of solution D and dilute to 1000 volumes with *water*.

Mobile phase B 10 volumes of solution A, 800 volumes of *acetonitrile* and dilute to 1000 volumes with *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	100	0	isocratic
1-11	100→80	0→20	linear gradient
11-31	80→0	20→100	linear gradient

www.webofpharma.com

https://thietbiuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
31-32	0→100	100→0	linear gradient
32-46	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to esomeprazole (retention time about 18 minutes) are: impurity 3, about 0.25; impurity 4, about 0.42; impurity 1, about 0.43; impurity A, about 0.5; impurity E, about 0.8; impurity D, about 0.95; impurity 2, about 1.1; impurity C, about 1.2, and impurity G, about 1.4 (2 peaks may be seen).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to impurity D and omeprazole is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder the contents of 20 sachets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) Shake a quantity of powdered granules containing the equivalent of 50 mg of esomeprazole with 200 mL of solution A, add 50 mL of *ethanol* and dilute to produce 500 mL with solution A. Dilute 1 volume to 25 volumes with a solution containing 1 volume of *ethanol*, 4 volumes of *water* and 20 volumes of solution A and filter (a 1-µm glass fibre filter is suitable).
(2) 0.002% w/v of *omeprazole BPCRS* in a mixture of 1 volume of *ethanol* and 4 volumes of solution A. Dilute 1 volume to 5 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

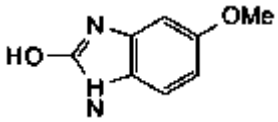
Calculate the content of $C_{17}H_{19}N_3O_3S$ in the granules using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LABELLING

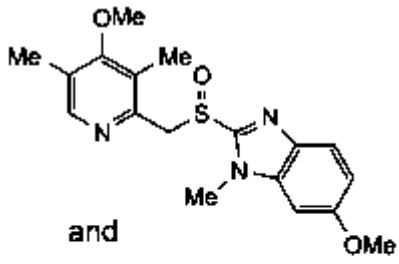
The quantity of active ingredient is stated in terms of the equivalent amount of esomeprazole.

IMPURITIES

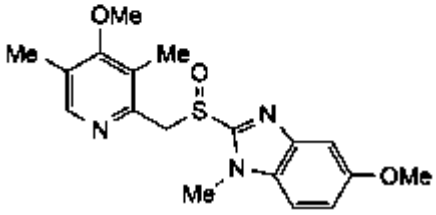
The impurities limited by the requirements of this monograph include impurities A, C, D and E listed under Esomeprazole Magnesium Dihydrate and Esomeprazole Magnesium Trihydrate, impurity G listed under Esomeprazole Sodium and:



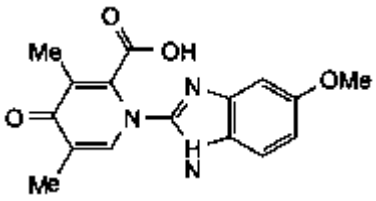
1. 2-hydroxy-5-methoxybenzimidazole (5-methoxy-2-benzimidazolinone),



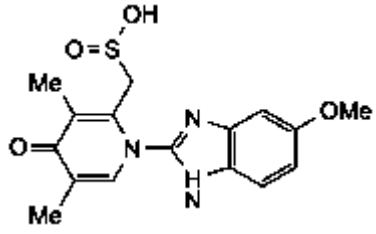
and



2. 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole, regioisomers,



3. 1,4-dihydro-1-(5-methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-2-pyridinecarboxylic acid,



www.webofpharma.com

https://thuocngocanh.com/

4. [1-(5-methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-4-oxo-1,4-dihydropyridin-2-yl] methanesulfinic acid.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Esomeprazole Gastro-resistant Tablets

General Notices

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Esomeprazole Gastro-resistant Tablets contain Esomeprazole Magnesium Dihydrate, Esomeprazole Magnesium Trihydrate or Esomeprazole Sodium. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of esomeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) Disperse a quantity of powdered tablets containing the equivalent of 40 mg of esomeprazole in 5 mL of *methanol*, dilute to 50 mL with solution A and filter (a 0.45-µm nylon filter is suitable). Further dilute 1 volume to 200 volumes with solution A.
(2) 0.0008% w/v of *omeprazole BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *α_1-acid-glycoprotein silica gel for chiral separation* (5 µm) (Chiralpak AGP is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 302 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

13 volumes of *acetonitrile* and 87 volumes of a solution containing 0.0025M *disodium hydrogen orthophosphate* and 0.005M *sodium dihydrogen orthophosphate*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to esomeprazole (retention time about 5 minutes) is: *(R)*-omeprazole (impurity F), about 0.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to *(R)*-omeprazole and esomeprazole is at least 3.0.

CONFIRMATION

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak due to esomeprazole in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak due to esomeprazole in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

Solution B 0.1 volumes of 10M *sodium hydroxide* and 10 volumes of *0.05M phosphate buffer solution pH 4.5*.

Solution C 5.2 volumes of 1M *anhydrous sodium dihydrogen orthophosphate* and 63.2 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate* and dilute to 1000 volumes with *water*. Adjust to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Use 700 mL of *0.05M phosphate buffer solution pH 4.5*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 60 minutes withdraw 5 mL of the medium and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the filtrate to 5 volumes with solution A and retain the samples for analysis. Proceed immediately to the final stage.
(2) 0.0002% w/v of *omeprazole BPCRS* in a mixture of 1 volume of solution A and 9 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (15 cm × 2 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable). Use a suitable guard column.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.25 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 302 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of solution C, 35 volumes of *water* and 40 volumes of *acetonitrile*, adjusted to pH 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of omeprazole is about 4 minutes.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of esomeprazole released is not more than 10% of the stated amount.

Final stage (pH 6.8)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 1 minute of withdrawing the medium at completion of the first stage, add 200 mL of solution B, at a temperature of 37°, to the vessel.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter (a 0.45-µm nylon filter is suitable). To a volume of the filtrate expected to contain the equivalent of 0.1 mg of esomeprazole, add 1 volume of 0.25M *sodium hydroxide* and dilute to 25 volumes with solution A.

(2) 0.002% w/v of *omeprazole BPCRS* in a mixture of 1 volume of solution A and 9 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is between 0.8 and 2.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of esomeprazole released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) To a quantity of powdered tablets containing the equivalent of 24 mg of esomeprazole, add 40 mL of *ethanol* and mix with the aid of ultrasound. Add 150 mL of solution A and further mix. Dilute with sufficient solution A to produce 250 mL and filter (a 0.45-µm nylon filter is suitable).

(2) Dilute 1 volume of solution (1) to 20 volumes with solution A. Dilute 1 volume of this solution to 10 volumes with *water*.

(3) 0.1% w/v of *omeprazole BPCRS* and 0.0005% w/v *omeprazole impurity D EPCRS*, each prepared by dissolving the reference material in 1 volume of *ethanol* and diluting to 5 volumes with solution A. Mix 1 volume of each solution and dilute to 10 volumes with *water*.

(4) Dilute 1 volume of solution (2) to 5 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil RP8 is suitable)

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 40 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of omeprazole.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of 0.14% w/v solution of *disodium hydrogen orthophosphate* previously adjusted to pH 7.6 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to omeprazole (retention time about 8 minutes) are: impurity 1, about 0.25; impurity A, about 0.35; impurity E, about 0.4; impurity D, about 0.8; impurity 2, about 1.7 and impurity C, about 4.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 11 volumes of 0.25M *trisodium orthophosphate*, 22 volumes of 0.5M *disodium hydrogen orthophosphate* and 67 volumes of *water*. Adjust to pH 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*.

(1) To a quantity of the powdered tablets containing the equivalent of 24 mg of esomeprazole, add 40 mL of *ethanol* and mix with the aid of ultrasound. Add 150 mL of solution A and further mix. Dilute with sufficient solution A to produce 250 mL and filter (a 0.45-µm nylon filter is suitable). Dilute 1 volume of the resulting solution to 10 volumes with *water*.
(2) 0.0096% w/v of *omeprazole BPCRS* prepared by dissolving the reference material in 1 volume of *ethanol* and diluting to 5 volumes with solution A. Dilute 1 volume of the resulting solution to 10 volumes with *water*.
(3) 0.1% w/v of *omeprazole BPCRS* and 0.0005% w/v *omeprazole impurity D EPCRS*, each prepared by dissolving the reference material in 1 volume of *ethanol* and diluting to 5 volumes with solution A. Mix 1 volume of each solution and dilute to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a detection wavelength of 302 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is greater than 5.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_3O_3S$ in the tablets using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LABELLING

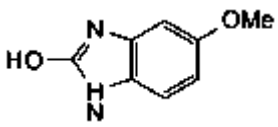
The quantity of active ingredient is stated in terms of the equivalent amount of esomeprazole.

IMPURITIES

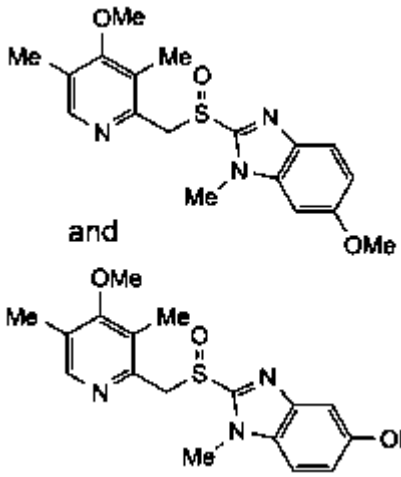
The impurities limited by the requirements of this monograph include impurities A, C, D and E listed under Esomeprazole Magnesium Dihydrate and Esomeprazole Magnesium Trihydrate and:

www.webofpharma.com

https://thuocngocanh.com/



1. 2-hydroxy-5-methoxybenzimidazole (5-methoxy-2-benzimidazolinone),



2. 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1-methyl-1*H*-benzimidazole, regioisomers.

© Crown Copyright 2022

www.webofpharma.com

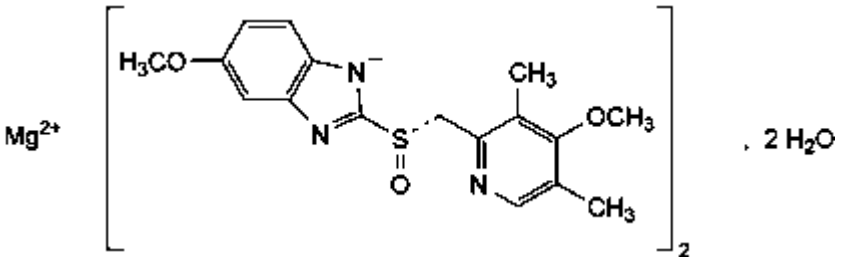
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Esomeprazole Magnesium Dihydrate

General Notices

(Ph. Eur. monograph 2787)



$C_{34}H_{36}MgN_6O_6S_2,2H_2O$ 749.2 *217087-10-0*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Preparations

Esomeprazole Gastro-resistant Capsules

Esomeprazole Gastro-resistant Tablets

Ph Eur

DEFINITION

Magnesium bis[5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazol-1-ide] dihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly coloured powder, slightly hygroscopic.

Solubility

Slightly soluble in water, soluble in methanol, practically insoluble in heptane.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison esomeprazole magnesium dihydrate CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

B. Enantiomeric purity (see Tests).

C. Ignite about 0.5 g of the substance to be examined according to the procedure for the sulfated ash test (2.4.14). Dissolve the residue in 10 mL of water R. 2 mL of this solution gives the reaction of magnesium (2.3.1).

D. Water (see Tests).

TESTS

Absorbance (2.2.25)

Maximum 0.20 at 440 nm.

Dissolve 0.500 g in methanol R and dilute to 25.0 mL with the same solvent. Filter through a membrane filter (nominal pore size 0.45 µm).

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure.

Buffer solution pH 6.0 Mix 20 mL of a 179.1 g/L solution of disodium hydrogen phosphate dodecahydrate R and 70 mL of a 156.0 g/L solution of sodium dihydrogen phosphate R, then dilute to 1000 mL with water R. Dilute 250 mL of this solution to 1000 mL with water R.

Buffer solution pH 11.0 Mix 11 mL of a 95.0 g/L solution of trisodium phosphate dodecahydrate R and 22 mL of a 179.1 g/L solution of disodium hydrogen phosphate dodecahydrate R, then dilute to 1000 mL with water R.

Test solution Dissolve 40 mg of the substance to be examined in 5 mL of methanol R and dilute to 50.0 mL with buffer solution pH 11.0. Dilute 1.0 mL of this solution to 25.0 mL with buffer solution pH 11.0.

Reference solution Dissolve 2 mg of omeprazole CRS in buffer solution pH 11.0 and dilute to 50.0 mL with the same buffer solution. Dilute 1.0 mL of the solution to 10.0 mL with buffer solution pH 11.0.

Column:

— *size*: *l* = 0.1 m, Ø = 4.0 mm;

— *stationary phase*: α_1-acid-glycoprotein silica gel for chiral separation R (5 µm).

Mobile phase acetonitrile R, buffer solution pH 6.0 (13:87 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 302 nm.

Injection 20 µL.

Relative retention With reference to esomeprazole (retention time = about 5 min): impurity F = about 0.7.

System suitability Reference solution:

— *resolution*: minimum 3.0 between the peaks due to impurity F and esomeprazole.

Limit:

— *impurity F*: maximum 0.6 per cent; disregard any peak other than impurity F and esomeprazole.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Prepare the solutions immediately before use.*

Test solution Dissolve 14 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 1 mg of *omeprazole CRS* and 1 mg of *omeprazole impurity D CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 3 mg of *omeprazole for peak identification CRS* (containing impurity E) in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 27 volumes of *acetonitrile R* and 73 volumes of a 1.4 g/L solution of *disodium hydrogen phosphate dodecahydrate R* previously adjusted to pH 7.6 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 40 µL.

Run time 4 times the retention time of esomeprazole.

Identification of impurities Use the chromatogram supplied with *omeprazole for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (a) to identify the

www.webofpharma.com

https://thuocngocanh.com/

peak due to impurity D.

Relative retention With reference to esomeprazole (retention time = about 9 min): impurity E = about 0.4; impurity D = about 0.7.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity D and omeprazole.

Limits:

— *impurities D, E*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Magnesium

3.30 per cent to 3.55 per cent (anhydrous substance).

Dissolve 0.400 g in 25 mL of *methanol R*, sonicate until dissolution is complete. Add 25 mL of *water R*, 10 mL of *concentrated ammonia R*, 20.000 mL of 0.05 M sodium edetate and about 50 mg of *mordant black 11 triturate R*. Titrate the excess of sodium edetate with *0.05 M zinc sulfate* until the colour changes from full blue to violet. Carry out a blank titration.

1 mL of 0.05 M sodium edetate corresponds to 1.21525 mg of Mg.

Water (*2.5.12*)

4.5 per cent to 6.1 per cent, determined on 0.200 g.

ASSAY

Liquid chromatography (*2.2.29*).

Buffer solution pH 11.0 Mix 11 mL of a 95.0 g/L solution of *trisodium phosphate dodecahydrate R* and 22 mL of a 179.1 g/L solution of *disodium hydrogen phosphate dodecahydrate R*, then dilute to 100.0 mL with *water R*.

Test solution Dissolve 10.0 mg of the substance to be examined in about 10 mL of *methanol R*, add 10 mL of buffer solution pH 11.0 and dilute to 200.0 mL with *water R*.

Reference solution Dissolve 10.0 mg of *omeprazole CRS* in about 10 mL of *methanol R*, add 10 mL of buffer solution pH 11.0 and dilute to 200.0 mL with *water R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of a 1.4 g/L solution of *disodium hydrogen phosphate dodecahydrate R* previously adjusted to pH 7.6 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 1.5 times the retention time of esomeprazole.

Retention time Esomeprazole = about 4 min.

Calculate the percentage content of $C_{34}H_{36}MgN_6O_6S_2$ taking into account the assigned content of *omeprazole CRS*.

1 g of omeprazole is equivalent to 1.032 g of esomeprazole magnesium.

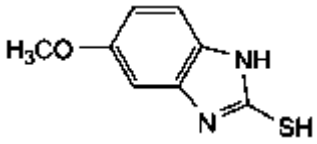
STORAGE

In an airtight container, protected from light.

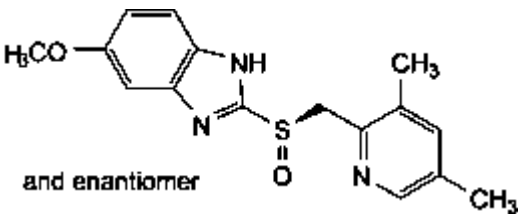
IMPURITIES

Specified impurities *D, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



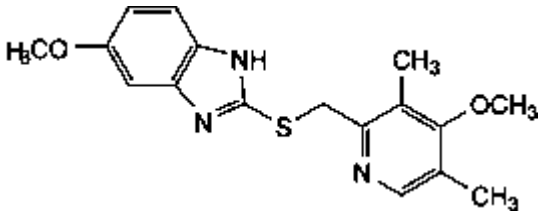
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



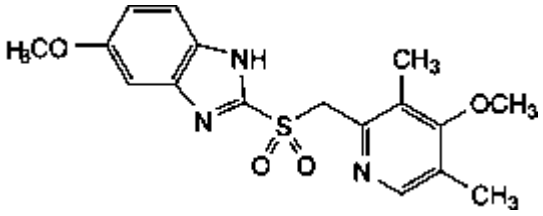
B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,

www.webofpharma.com

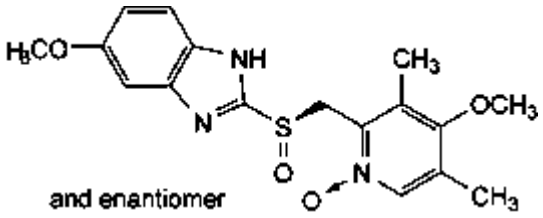
https://thuocngocanh.com/



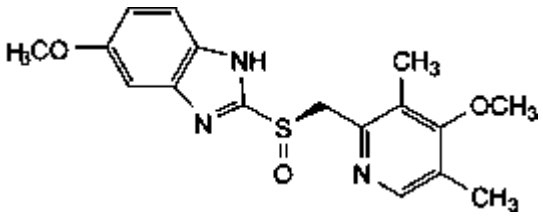
C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),



D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole sulfone),



E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide,



F. 5-methoxy-2-[(*R*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole ((*R*)-omeprazole).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

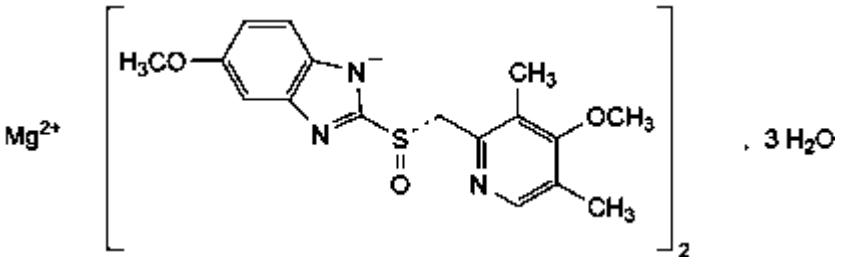
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Esomeprazole Magnesium Trihydrate

General Notices

(Ph. Eur. monograph 2372)



$C_{34}H_{36}MgN_6O_6S_2,3H_2O$ 767.2

217087-09-7

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Preparations

Esomeprazole Gastro-resistant Capsules

Esomeprazole Gastro-resistant Granules

Esomeprazole Gastro-resistant Tablets

Ph Eur

DEFINITION

Magnesium bis[5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazol-1-ide] trihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or slightly coloured powder, slightly hygroscopic.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Slightly soluble in water, soluble in methanol, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison esomeprazole magnesium trihydrate CRS.

B. Enantiomeric purity (see Tests).

C. Ignite about 0.5 g of the substance to be examined according to the procedure for the sulfated ash test (2.4.14). Dissolve the residue in 10 mL of water R. 2 mL of this solution gives the reaction of magnesium (2.3.1).

D. Water (see Tests).

TESTS

Absorbance (2.2.25)

Maximum 0.20 at 440 nm.

Dissolve 0.500 g in methanol R and dilute to 25.0 mL with the same solvent. Filter through a membrane filter (nominal pore size 0.45 µm).

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure.

Buffer solution pH 6.0 Mix 20 mL of a 179.1 g/L solution of disodium hydrogen phosphate dodecahydrate R and 70 mL of a 156.0 g/L solution of sodium dihydrogen phosphate R, then dilute to 1000 mL with water R. Dilute 250 mL of this solution to 1000 mL with water R.

Buffer solution pH 11.0 Mix 11 mL of a 95.0 g/L solution of trisodium phosphate dodecahydrate R and 22 mL of a 179.1 g/L solution of disodium hydrogen phosphate dodecahydrate R, then dilute to 1000 mL with water R.

Test solution Dissolve 40 mg of the substance to be examined in 5 mL of methanol R and dilute to 50.0 mL with buffer solution pH 11.0. Dilute 1.0 mL of this solution to 25.0 mL with buffer solution pH 11.0.

Reference solution Dissolve 2 mg of omeprazole CRS in buffer solution pH 11.0 and dilute to 50.0 mL with the same buffer solution. Dilute 1.0 mL of the solution to 10.0 mL with buffer solution pH 11.0.

Column:

— *size*: *l* = 0.1 m, Ø = 4.0 mm;

— *stationary phase*: α_1-acid-glycoprotein silica gel for chiral separation R (5 µm).

Mobile phase acetonitrile R, buffer solution pH 6.0 (13:87 *V/V*).

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 302 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL.

Relative retention With reference to esomeprazole (retention time = about 5 min): impurity F = about 0.7.

System suitability Reference solution:

— *resolution*: minimum 3.0 between the peaks due to impurity F and esomeprazole.

Limit:

— *impurity F*: maximum 0.2 per cent; disregard any peak other than impurity F and esomeprazole.

Related substances

Liquid chromatography (2.2.29): use the normalisation procedure. *Prepare the solutions immediately before use.*

Test solution Dissolve 14 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 1 mg of *omeprazole CRS* and 1 mg of *omeprazole impurity D CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 3 mg of *omeprazole for peak identification CRS* (containing impurity E) in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 27 volumes of *acetonitrile R* and 73 volumes of a 1.4 g/L solution of *disodium hydrogen phosphate dodecahydrate R* previously adjusted to pH 7.6 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 40 µL.

Run time 4 times the retention time of esomeprazole.

Identification of impurities Use the chromatogram supplied with *omeprazole for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity E; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to esomeprazole (retention time = about 9 min): impurity E = about 0.4; impurity D = about 0.7.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity D and omeprazole.

Limits:

— *impurities D, E*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Magnesium

3.30 per cent to 3.55 per cent (anhydrous substance).

Dissolve 0.400 g in 25 mL of *methanol R*, sonicate until dissolution is complete. Add 25 mL of *water R*, 10 mL of *concentrated ammonia R*, 20.000 mL of 0.05 M sodium edetate and about 50 mg of *mordant black 11 triturate R*. Titrate the excess of sodium edetate with *0.05 M zinc sulfate* until the colour changes from full blue to violet. Carry out a blank titration.

1 mL of 0.05 M sodium edetate corresponds to 1.21525 mg of Mg.

Water (*2.5.12*)

6.2 per cent to 8.0 per cent, determined on 0.200 g.

ASSAY

Liquid chromatography (*2.2.29*).

Buffer solution pH 11.0 Mix 11 mL of a 95.0 g/L solution of *trisodium phosphate dodecahydrate R* and 22 mL of a 179.1 g/L solution of *disodium hydrogen phosphate dodecahydrate R*, then dilute to 100.0 mL with *water R*.

Test solution Dissolve 10.0 mg of the substance to be examined in about 10 mL of *methanol R*, add 10 mL of buffer solution pH 11.0 and dilute to 200.0 mL with *water R*.

Reference solution Dissolve 10.0 mg of *omeprazole CRS* in about 10 mL of *methanol R*, add 10 mL of buffer solution pH 11.0 and dilute to 200.0 mL with *water R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 35 volumes of *acetonitrile R* and 65 volumes of a 1.4 g/L solution of *disodium hydrogen phosphate dodecahydrate R* previously adjusted to pH 7.6 with *phosphoric acid R*.

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 1.5 times the retention time of esomeprazole.

Retention time Esomeprazole = about 4 min.

Calculate the percentage content of $C_{34}H_{36}MgN_6O_6S_2$ taking into account the assigned content of *omeprazole CRS*.

1 g of omeprazole is equivalent to 1.032 g of esomeprazole magnesium.

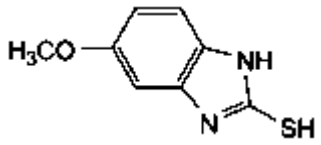
STORAGE

In an airtight container, protected from light.

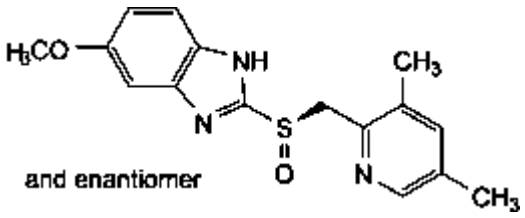
IMPURITIES

Specified impurities *D, E, F.*

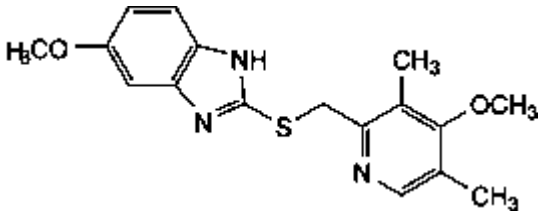
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



A. 5-methoxy-1*H*-benzimidazole-2-thiol,



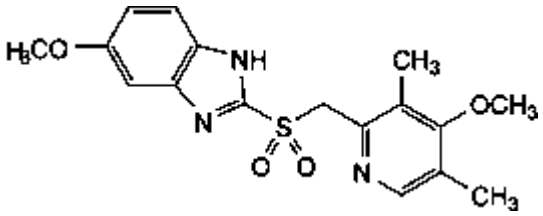
B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



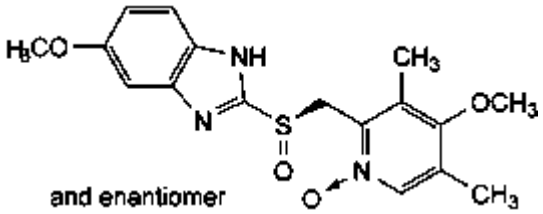
www.webofpharma.com

https://thuocngocanh.com/

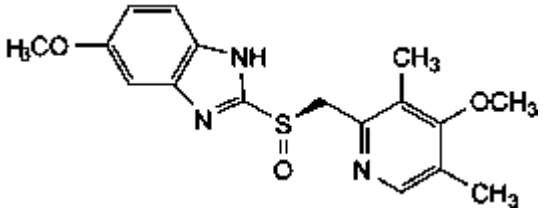
C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),



D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole sulfone),



E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide,



F. 5-methoxy-2-[(*R*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1*H*-benzimidazole ((*R*)-omeprazole).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

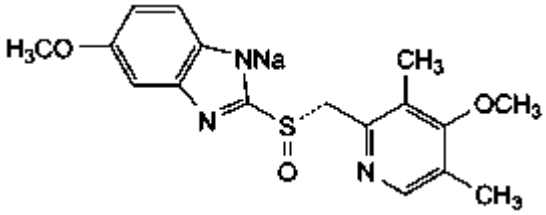
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Esomeprazole Sodium

General Notices

(Ph. Eur. monograph 2923)



$C_{17}H_{18}N_3NaO_3S$ 367.4 *161796-78-7*

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

Preparations

Esomeprazole Gastro-resistant Capsules

Esomeprazole Gastro-resistant Tablets

Ph Eur

DEFINITION

Sodium 5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1*H*-benzimidazol-1-ide.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, amorphous or crystalline powder, slightly hygroscopic.

Solubility

Freely soluble in water and in ethanol (96 per cent), soluble in propylene glycol, very slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison esomeprazole sodium CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in ethanol (96 per cent) R, evaporate to dryness and record new spectra using the residues.

B. Enantiomeric purity (see Tests).

C. Ignite 1 g and cool. Add 1 mL of water R to the residue and neutralise with hydrochloric acid R. Filter and dilute the filtrate to 4 mL with water R. 0.1 mL of the solution gives reaction (b) of sodium (2.3.1).

TESTS

Solution S

Dissolve 0.50 g in carbon dioxide-free water R and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, Method II).

pH (2.2.3)

10.3 to 11.3 for solution S.

Enantiomeric purity

Liquid chromatography (2.2.29): use the normalisation procedure. *Prepare the solutions immediately before use.*

Buffer solution pH 6.0 Mix 20 mL of a 179.1 g/L solution of disodium hydrogen phosphate dodecahydrate R and 70 mL of a 156.0 g/L solution of sodium dihydrogen phosphate R, then dilute to 1000.0 mL with water for chromatography R. Dilute 250 mL of this solution to 1000.0 mL with water for chromatography R.

Buffer solution pH 11.0 Mix 11 mL of a 95.0 g/L solution of trisodium phosphate dodecahydrate R and 22 mL of a 179.1 g/L solution of disodium hydrogen phosphate dodecahydrate R, then dilute to 1000.0 mL with water R.

Test solution Dissolve 40 mg of the substance to be examined in buffer solution pH 11.0 and dilute to 50.0 mL with the same buffer solution. Dilute 1.0 mL of this solution to 25.0 mL with buffer solution pH 11.0.

Reference solution (a) Dissolve 2 mg of omeprazole CRS in buffer solution pH 11.0 and dilute to 50 mL with the same buffer solution. Dilute 1 mL of the solution to 10 mL with buffer solution pH 11.0.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with buffer solution pH 11.0. Dilute 1.0 mL of this solution to 20.0 mL with buffer solution pH 11.0.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *α$_1$-acid-glycoprotein silica gel for chiral separation R* (5 µm).

Mobile phase *acetonitrile R*, buffer solution pH 6.0 (15:85 *V/V*).

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 302 nm.

Injection 20 µL.

Run time 1.5 times the retention time of esomeprazole.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to esomeprazole (retention time = about 4 min): impurity B = about 0.7.

System suitability Reference solution (a):

— *resolution*: minimum 2.8 between the peaks due to impurity B and esomeprazole.

Limit:

— *impurity B*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)); disregard any peak other than impurity B and esomeprazole.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Buffer solution pH 7.6 Dissolve 5.7 g of *disodium hydrogen phosphate dihydrate R* and 0.7 g of *sodium dihydrogen phosphate monohydrate R* in *water for chromatography R* and dilute to 1000.0 mL with the same solvent.

Test solution Dissolve 10 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 1 mg of *omeprazole CRS* and 1 mg of *omeprazole impurity D CRS* in mobile phase A and dilute to 50 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: mix 100 mL of *acetonitrile R* and 100 mL of buffer solution pH 7.6 and dilute to 1000.0 mL with *water for chromatography R*;

— *mobile phase B*: mix 10 mL of buffer solution pH 7.6 and 800 mL of *acetonitrile R* and dilute to 1000.0 mL with *water for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 12	100 → 80	0 → 20
12 - 32	80 → 0	20 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 302 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to esomeprazole (retention time = about 16 min): impurity D = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity D and omeprazole.

Calculation of percentage contents:

— for each impurity, use the concentration of esomeprazole sodium in reference solution (b).

Limits:

— *impurity D*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.300 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.300 g in 50 mL of *carbon dioxide-free water R*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 36.74 mg of $C_{17}H_{18}N_3NaO_3S$.

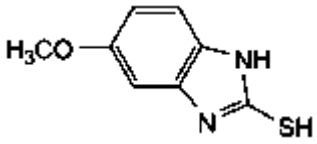
STORAGE

In an airtight container, protected from light.

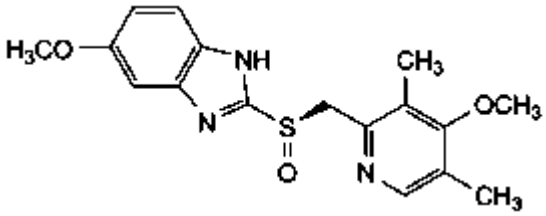
IMPURITIES

Specified impurities *B, D.*

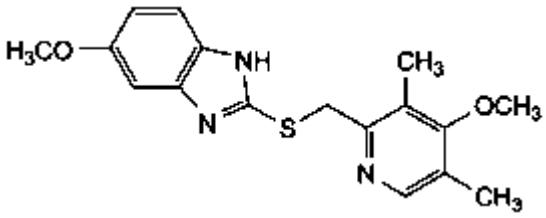
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, E, F, G.*



A. 5-methoxy-1*H*-benzimidazole-2-thiol,



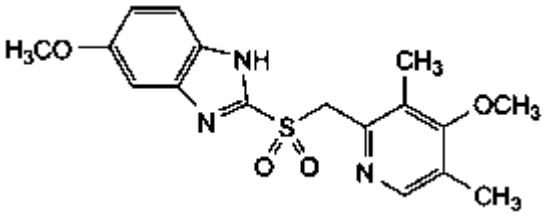
B. 5-methoxy-2-[(*R*)-(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1*H*-benzimidazole ((*R*)-omeprazole),



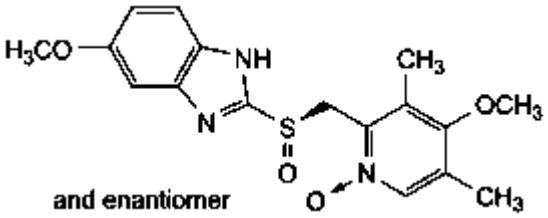
C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),

www.webofpharma.com

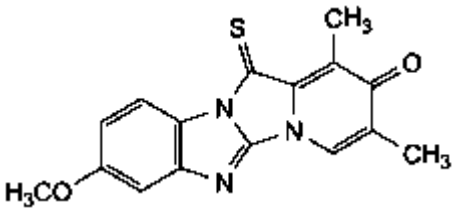
https://thuocngocanh.com/



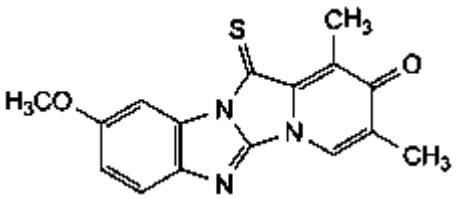
D. 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfonyl]-1*H*-benzimidazole (omeprazole sulfone),



E. 4-methoxy-2-[[(*RS*)-5-methoxy-1*H*-benzimidazole-2-sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide,



F. 8-methoxy-1,3-dimethyl-12-sulfanylidenepyrido[1′,2′:3,4]imidazo[1,2-a]benzimidazol-2(12*H*)-one,



G. 9-methoxy-1,3-dimethyl-12-sulfanylidenepyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estradiol and Norethisterone Acetate Tablets

General Notices

Action and use

Estrogen.

DEFINITION

Estradiol and Norethisterone Acetate Tablets contain Estradiol Hemihydrate and Norethisterone Acetate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of estradiol, $C_{18}H_{24}O_2$ and norethisterone acetate, $C_{22}H_{28}O_3$

Content		Limits	
Estradiol mg	Norethisterone Acetate mg	Estradiol % of stated amount	Norethisterone Acetate % of stated amount
2	1	95.0 to 105.0	92.5 to 105.0
1	1	95.0 to 105.0	92.5 to 105.0
1	0.5	95.0 to 105.0	92.5 to 105.0
0.5	0.1	95.0 to 105.0	90.0 to 105.0

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 0.2 mL of *water* to two tablets and shake to disperse. Add sufficient *ethanol (96%)* to produce a solution containing 0.035% w/v of Norethisterone Acetate, centrifuge and use the clear supernatant liquid.

(2) A suitable concentration of *estradiol hemihydrate BPCRS* and *norethisterone acetate BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and spray with *ethanolic sulfuric acid (5%)*. Heat the plate at 105° for 15 minutes and examine under *ultraviolet light (365 nm)*.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (1) shows two clearly separated spots.

CONFIRMATION

The two principal spots in the chromatogram obtained with solution (1) correspond in position and colour to those in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) shows two peaks having the same retention times as the peaks due to estradiol and norethisterone acetate in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of a 0.3% w/v solution of *sodium lauryl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with a 0.3% w/v solution of *sodium lauryl sulfate* if necessary, to produce a solution expected to contain 0.0001% w/v of estradiol.

(2) Dissolve sufficient quantities of *estradiol hemihydrate BPCRS* and *norethisterone acetate BPCRS* in a 0.3% w/v solution of *sodium lauryl sulfate* and dilute with a sufficient volume of a 0.3% w/v solution of *sodium lauryl sulfate* to produce concentrations in the final solution the same as those expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

450 volumes of *water* and 550 volumes of *acetonitrile*.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between each pair of peaks (estradiol and norethisterone, and estrone and norethisterone acetate) is at least 1.0.

DETERMINATION OF CONTENT

Calculate the total content of estradiol, $C_{18}H_{24}O_2$, and of norethisterone acetate, $C_{22}H_{28}O_3$, in the medium using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS* and the declared content of $C_{22}H_{28}O_3$ in *norethisterone acetate BPCRS*.

Estrone and norethisterone

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) Add 20 mL of the mobile phase to a quantity of the powdered tablets containing 5 mg of Estradiol, mix with the aid of ultrasound and add sufficient mobile phase to produce 25 mL. Centrifuge and use the clear supernatant liquid.
(2) Add 20 mL of the mobile phase to a quantity of the powdered tablets containing 2.5 mg of Norethisterone Acetate, mix with the aid of ultrasound and add sufficient mobile phase to produce 25 mL. Centrifuge and use the clear supernatant liquid.
(3) 0.0001% w/v of *estrone BPCRS*.
(4) 0.00005% w/v of *norethisterone BPCRS*.
(5) 0.0017% w/v of *estradiol hemihydrate BPCRS*, 0.00084% w/v of *norethisterone acetate BPCRS*, 0.00066% w/v of *estrone BPCRS* and 0.00034% w/v of *norethisterone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but injecting 20 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution factor* between each pair of peaks (estradiol and norethisterone, and estrone and norethisterone acetate) is at least 1.0.

LIMITS

In the chromatogram obtained with solution (1) quantify the area of any peak due to estrone using the principal peak in the chromatogram obtained with solution (3).

In the chromatogram obtained with solution (2) quantify the area of any peak due to norethisterone using the principal peak in the chromatogram obtained with solution (4).

www.webofpharma.com

https://thuocngocanh.com/

Content of		Limits	
Estradiol mg	Norethisterone Acetate mg	Estrone %	Norethisterone %
2	1	0.5	0.5
1	1	0.5	0.5
1	0.5	0.5	0.5
0.5	0.1	0.5	1.0

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of estradiol or less than 2 mg and/or less than 2% w/w of Norethisterone Acetate comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of the mobile phase to one tablet, mix with the aid of ultrasound, cool, add sufficient of the mobile phase to produce 25 mL and centrifuge. Dilute the supernatant liquid if necessary, with the mobile phase to produce a solution containing the equivalent of 0.002% w/v of estradiol.

(2) Dissolve sufficient quantities of *estradiol hemihydrate BPCRS* and *norethisterone acetate BPCRS* in the mobile phase and dilute with sufficient mobile phase to produce concentrations in the final solution the same as those expected for solution (1).

(3) 0.0017% w/v of *estradiol hemihydrate BPCRS*, 0.00084% w/v of *norethisterone acetate BPCRS*, 0.00066% w/v of *estrone BPCRS* and 0.00034% w/v of *norethisterone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but injecting 20 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between each pair of peaks (estradiol and norethisterone, and estrone and norethisterone acetate) is at least 1.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{24}O_2$ and of $C_{22}H_{28}O_3$ in each tablet using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS* and the declared content of $C_{22}H_{28}O_3$ in *norethisterone acetate BPCRS*.

ASSAY

For estradiol

For tablets containing less than 2 mg and/or less than 2% w/w of estradiol

Use the average of the 10 individual results obtained in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of estradiol

www.webofpharma.com

https://thuocngocanh.com/

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Add 50 mL of the mobile phase to a quantity of powdered tablets containing the equivalent of 10 mg of estradiol, mix with the aid of ultrasound and centrifuge. Dilute 10 mL of the clear supernatant liquid to 100 mL with the mobile phase.

(2) 0.002% w/v of *estradiol hemihydrate BPCRS*.

(3) 0.0017% w/v of *estradiol hemihydrate BPCRS*, 0.00084% w/v of *norethisterone acetate BPCRS*, 0.00066% w/v of *estrone BPCRS* and 0.00034% w/v of *norethisterone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but injecting 20 µL of each solution.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution factor* between each pair of peaks (estradiol and norethisterone, and estrone and norethisterone acetate) is at least 1.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{24}O_2$ in each tablet using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS*.

For norethisterone acetate

For tablets containing less than 2 mg and/or less than 2% w/w of estradiol

Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

Estradiol and Norethisterone Acetate Tablets should be protected from light.

LABELLING

The label states the quantity of estradiol hemihydrate in terms of the equivalent amount of estradiol.

IMPURITIES

The impurities limited by the requirements of this monograph include:

A. Estrone,

B. Norethisterone.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estradiol and Norethisterone Tablets

General Notices

Action and use

Estrogen.

DEFINITION

Estradiol and Norethisterone Tablets contain Estradiol Hemihydrate and Norethisterone. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of estradiol, $C_{18}H_{24}O_2$

95.0 to 105.0% of the stated amount.

Content of norethisterone, $C_{20}H_{26}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Add 0.2 mL of *water* to two tablets and shake to disperse. Add sufficient *ethanol (96%)* to produce a solution containing 0.035% w/v of Norethisterone, centrifuge and use the clear supernatant liquid.

(2) A suitable concentration of *estradiol hemihydrate BPCRS* and *norethisterone BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air and spray with *ethanolic sulfuric acid (5%)*. Heat the plate at 105° for 15 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of *dichloromethane*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The chromatogram obtained with solution (1) shows two clearly separated spots with R_f values corresponding to those observed in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) shows two peaks having the same retention times as those due to estradiol and norethisterone in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 500 mL of a 0.3% w/v solution of *sodium lauryl sulfate* in *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter, discarding the first 5 mL of the filtrate. Use the filtered medium.
(2) Dissolve a sufficient quantity of *estradiol hemihydrate BPCRS* and *norethisterone BPCRS* in *methanol (80%)* and dilute an aliquot with a 0.3% w/v solution of *sodium lauryl sulfate* in *water*; the concentration of the final solution should be the same as that expected for solution (1).
(3) 0.0017% w/v of *estradiol hemihydrate BPCRS*, 0.00084% w/v of *norethisterone acetate BPCRS*, 0.00066% w/v of *estrone BPCRS* and 0.00034% w/v of *norethisterone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 235 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

450 volumes of *water* and 550 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between each pair of peaks (estradiol and norethisterone, and estrone and norethisterone acetate) is at least 1.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of estradiol, $C_{18}H_{24}O_2$, and norethisterone, $C_{20}H_{26}O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS* and $C_{20}H_{26}O_2$ in *norethisterone BPCRS*.

Estrone

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Powder 20 tablets. Add 20 mL of the mobile phase to a quantity of the powdered tablets containing the equivalent of 5 mg of estradiol, mix with the aid of ultrasound and add sufficient mobile phase to produce 25 mL. Centrifuge and use the clear supernatant liquid.
(2) 0.0001% w/v of *estrone BPCRS* in the mobile phase.
(3) 0.0017% w/v of *estradiol hemihydrate BPCRS*, 0.00084% w/v of *norethisterone acetate BPCRS*, 0.00066% w/v of *estrone BPCRS* and 0.00034% w/v of *norethisterone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but using an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between each pair of peaks (estradiol and norethisterone, and estrone and norethisterone acetate) is at least 1.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to estrone is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Uniformity of content

Tablets containing less than the equivalent of 2 mg and/or less than 2% w/w of estradiol comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 20 mL of the mobile phase to one tablet, mix with the aid of ultrasound, cool, add sufficient of the mobile phase to produce 25 mL and centrifuge. Dilute the supernatant liquid, if necessary, with the mobile phase to produce a solution containing the equivalent of 0.002% w/v of estradiol.
(2) Dissolve sufficient quantities of *estradiol hemihydrate BPCRS* and *norethisterone BPCRS* in the mobile phase and dilute an aliquot with the mobile phase; the concentrations in the final solution are the same as those expected for solution (1).
(3) 0.0017% w/v of *estradiol hemihydrate BPCRS*, 0.00084% w/v of *norethisterone acetate BPCRS*, 0.00066% w/v of *estrone BPCRS* and 0.00034% w/v of *norethisterone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but using an injection volume of 20 µL.

SYSTEM SUITABILITY

www.webofpharma.com

https://nhathuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between each pair of peaks (estradiol and norethisterone, and estrone and norethisterone acetate) is at least 1.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{24}O_2$ and $C_{20}H_{26}O_2$ in each tablet using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS* and the declared content of $C_{20}H_{26}O_2$ in *norethisterone BPCRS*.

ASSAY

For estradiol

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of estradiol

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of estradiol

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of the mobile phase to a quantity of powdered tablets containing the equivalent of 10 mg of estradiol, mix with the aid of ultrasound and centrifuge. Dilute 1 volume of the clear supernatant liquid to 10 volumes with mobile phase.
(2) 0.002% w/v of *estradiol hemihydrate BPCRS* in the mobile phase.
(3) 0.0017% w/v of *estradiol hemihydrate BPCRS*, 0.00084% w/v of *norethisterone acetate BPCRS*, 0.00066% w/v of *estrone BPCRS* and 0.00034% w/v of *norethisterone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used, but using an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between each pair of peaks (estradiol and norethisterone, and estrone and norethisterone acetate) is at least 1.0.

DETERMINATION OF CONTENT

Calculate the total content of estradiol, $C_{18}H_{24}O_2$, in the tablets using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS*.

For norethisterone

Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

Estradiol and Norethisterone Tablets should be protected from light.

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The quantity of Estradiol Hemihydrate is stated in terms of the equivalent amount of estradiol.

IMPURITIES

The impurities limited by the requirements of this monograph include:

A. Estrone.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

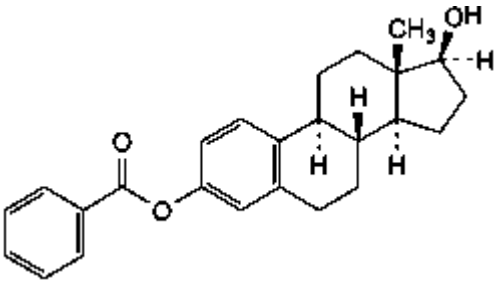
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estradiol Benzoate

General Notices

(Ph. Eur. monograph 0139)



$C_{25}H_{28}O_3$ 376.5 *50-50-0*

Action and use

Estrogen.

Ph Eur

DEFINITION

17β-Hydroxyestra-1,3,5(10)-trien-3-yl benzoate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

Almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *estradiol benzoate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Specific optical rotation (*2.2.7*)

+ 55.0 to + 59.0 (dried substance).

Dissolve 0.250 g in *acetone R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20 mg of the substance to be examined in *acetonitrile R1* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *estradiol benzoate for system suitability CRS* (containing impurities A, B, C, E and G) in *acetonitrile R1* and dilute to 2.5 mL with the same solvent.

Reference solution (b) Dilute 0.5 mL of the test solution to 100.0 mL with *acetonitrile R1*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water R*, *acetonitrile R1* (40:60 *V/V*);

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 21	100 → 10	0 → 90
21 - 31	10	90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *estradiol benzoate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, E and G.

Relative retention With reference to estradiol benzoate (retention time = about 19 min): impurity A = about 0.3; impurity E = about 1.1; impurity B = about 1.2; impurity G = about 1.3; impurity C = about 1.5.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to estradiol benzoate.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 3.3; impurity C = 0.7;

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurities B, E, G*: for each impurity, not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity A*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 25.0 mg in *anhydrous ethanol R* and dilute to 250.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *anhydrous ethanol R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 231 nm.

Calculate the content of $C_{25}H_{28}O_3$ taking the specific absorbance to be 500.

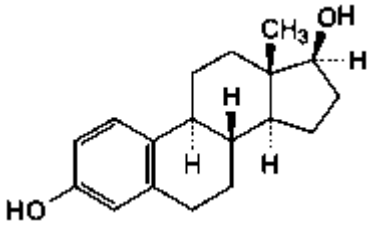
IMPURITIES

Specified impurities *A, B, C, E, G.*

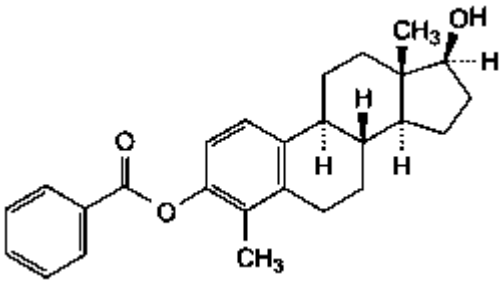
www.webofpharma.com

https://thuocngocanh.com/

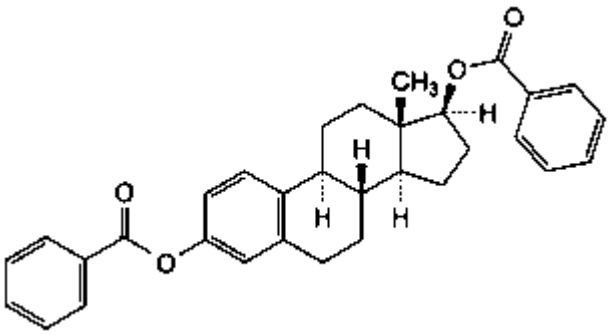
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, F, H.



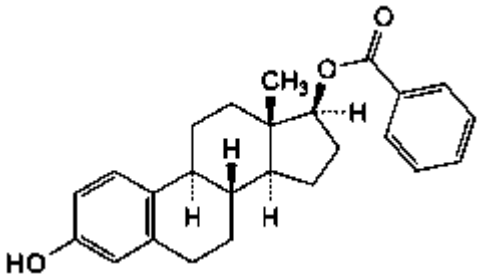
A. estra-1,3,5(10)-triene-3,17β-diol (estradiol),



B. 17β-hydroxy-4-methylestra-1,3,5(10)-trien-3-yl benzoate,



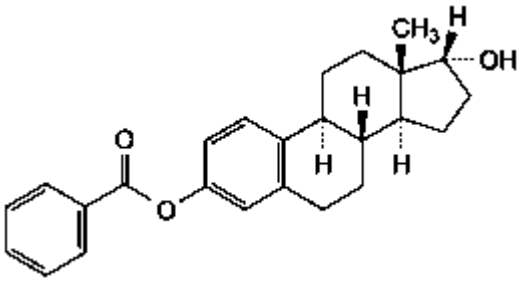
C. estra-1,3,5(10)-triene-3,17β-diyl dibenzoate,



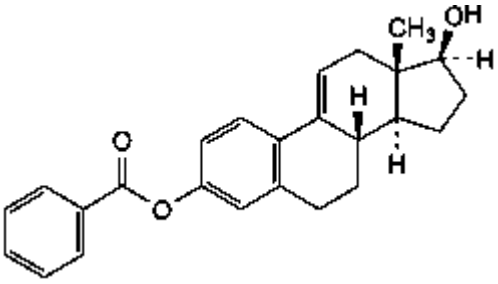
D. 3-hydroxyestra-1,3,5(10)-trien-17β-yl benzoate,

www.webofpharma.com

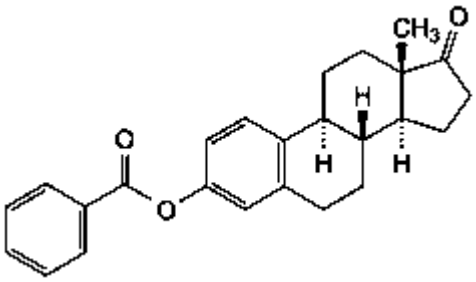
https://thuocngocanh.com/



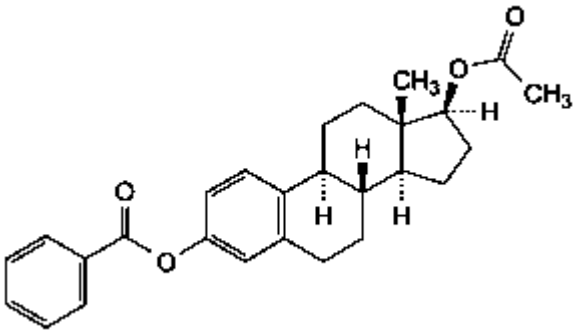
E. 17α-hydroxyestra-1,3,5(10)-trien-3-yl benzoate,



F. 17β-hydroxyestra-1,3,5(10),9(11)-tetraen-3-yl benzoate.



G. 17-oxoestra-1,3,5(10)-trien-3-yl benzoate (estrone benzoate),



H. estra-1,3,5(10)-triene-3,17β-diyl 17-acetate 3-benzoate,

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

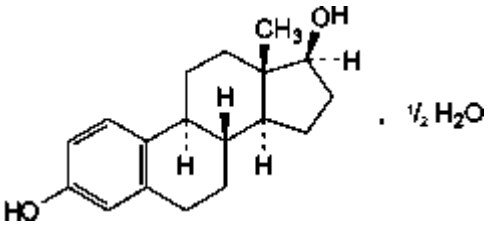
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estradiol Hemihydrate

General Notices

(Ph. Eur. monograph 0821)



$C_{18}H_{24}O_2,½H_2O$ 281.4

Action and use

Estrogen.

Preparations

Estradiol Transdermal Patches

Estradiol and Norethisterone Tablets

Estradiol and Norethisterone Acetate Tablets

Estradiol Vaginal Tablets

Ph Eur

DEFINITION

Estra-1,3,5(10)-triene-3,17β-diol hemihydrate.

Content

97.0 per cent to 103.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A, C, D, E.

A. Melting point (2.2.14): 175 °C to 180 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *estradiol hemihydrate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 50 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of *estradiol hemihydrate CRS* in *methanol R* and dilute to 50 mL with the same solvent.

Reference solution (b) Dissolve 25 mg of *ethinylestradiol CRS* in reference solution (a) and dilute to 25 mL with reference solution (a).

Plate *TLC silica gel plate R*.

Mobile phase *ethanol (96 per cent) R*, *toluene R* (20:80 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air until the solvent has evaporated.

Detection Heat at 110 °C for 10 min. Spray the hot plate with *alcoholic solution of sulfuric acid R*. Heat again at 110 °C for 10 min. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

System suitability The chromatogram obtained with reference solution (b) shows 2 spots which may however not be completely separated.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

D. To about 1 mg add 0.5 mL of freshly prepared *sulfomolybdic reagent R2*. A blue colour develops which in ultraviolet light at 365 nm has an intense green fluorescence. Add 1 mL of *sulfuric acid R* and 9 mL of *water R*. The colour becomes pink with a yellowish fluorescence.

E. Water (see Tests).

TESTS

Specific optical rotation (2.2.7)

+ 76.0 to + 83.0 (anhydrous substance).

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.250 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of *acetonitrile R* and dilute to 25.0 mL with *methanol R2*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Mix equal volumes of a 1 mg/mL solution of the substance to be examined in *methanol R2* and of a 1 mg/mL solution of *2,3-dichloro-5,6-dicyanobenzoquinone R* in *methanol R2*. Allow to stand for 30 min before injection.

Reference solution (c) Dissolve 5 mg of *estradiol for peak identification CRS* (containing impurities A, B and C) in 2 mL of *acetonitrile R* and dilute to 5.0 mL with *methanol R2*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase To 400 mL of *acetonitrile R* add 50 mL of *methanol R2* and 400 mL of *water for chromatography R*; allow to stand for 10 min, dilute to 1000 mL with *water for chromatography R* and mix again.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time Twice the retention time of estradiol.

Identification of impurities Use the chromatogram supplied with *estradiol for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to estradiol (retention time = about 13 min): impurity D = about 0.9; impurity B = about 1.1; impurity A = about 1.4; impurity C = about 1.9.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to estradiol and impurity B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity D by 0.4;

www.webofpharma.com

https://thuocngocanh.com/

— *impurities A, B, C, D*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

2.9 per cent to 3.5 per cent, determined on 0.500 g.

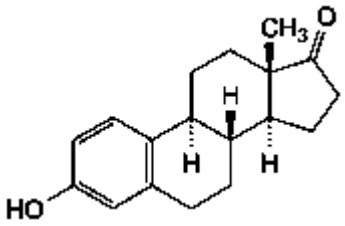
ASSAY

Dissolve 20.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *0.1 M sodium hydroxide*. Allow to cool to room temperature. Measure the absorbance (*2.2.25*) of the solution at the maximum at 238 nm.

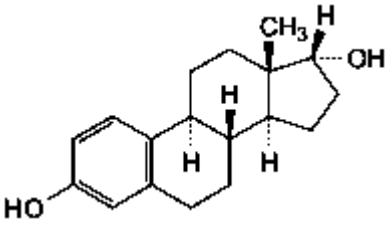
Calculate the content of $C_{18}H_{24}O_2$ taking the specific absorbance to be 335.

IMPURITIES

Specified impurities *A, B, C, D.*



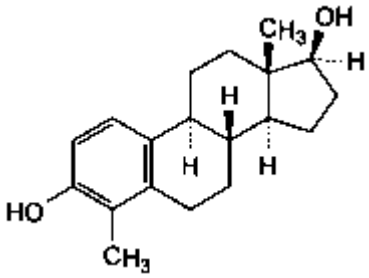
A. 3-hydroxyestra-1,3,5(10)-trien-17-one (estrone),



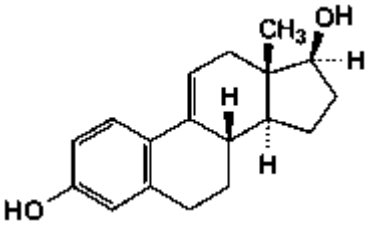
B. estra-1,3,5(10)-triene-3,17α-diol (17α-estradiol),

www.webofpharma.com

https://thuathuocngocanh.com/



C. 4-methylestra-1,3,5(10)-triene-3,17β-diol,



D. estra-1,3,5(10),9(11)-tetraene-3,17β-diol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estradiol Transdermal Patches

General Notices

Action and use

Estrogen.

DEFINITION

Estradiol Transdermal Patches contain Estradiol Hemihydrate in a suitable matrix or reservoir presentation.

PRODUCTION

A suitable test is carried out to demonstrate the appropriate release of estradiol.

The transdermal patches comply with the requirements stated under Transdermal Patches and with the following requirements.

Content of estradiol, $C_{18}H_{24}O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Remove the release liner from a patch, score the exposed surface and cover the sticky surface with a small piece of glass wool. Place the patch in a centrifuge tube and add sufficient *methanol* to produce a solution containing the equivalent of 2 mg of estradiol in 5 mL of solvent, mix with the aid of ultrasound, shake for 15 minutes and, if necessary, filter through a glass-fibre filter paper (Whatman GF/C is suitable) followed by a 0.45-µm membrane filter.

(2) 0.04% w/v of *estradiol hemihydrate BPCRS* in *absolute ethanol*, dissolved with the aid of ultrasound.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (100 mm × 100 mm) (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 7 cm.

(e) After removal of the plate, dry in a stream of warm air for 5 minutes, spray with *methanolic sulfuric acid (50%)* and heat at 110° for 10 minutes. Allow to cool and examine under *ultraviolet light (366 nm)*.

MOBILE PHASE

2 volumes of *acetone* and 8 volumes of *dichloromethane*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Remove the release liners from 10 patches, score the exposed surfaces and cover the sticky surfaces with small pieces of glass wool. Place the patches in a flask containing sufficient mobile phase to produce a solution containing the equivalent of 0.01% w/v of estradiol, mix with the aid of ultrasound for 10 minutes, shake mechanically for 1 hour and filter through a glass-fibre filter paper (Whatman GF/C is suitable). If the filtrate is not clear, filter it through a membrane filter with a pore size of 0.45 µm.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecysilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 50 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *signal to-noise ratio* for the peak due to Estradiol is at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak due to diethyltoluamide.

www.webofpharma.com

https://thuocngocanh.com/

Uniformity of content

Comply with the requirements stated under *uniformity of content*, Appendix XII C3, Test C, with respect to the individual content of each dosage unit and using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Remove the release liner from a patch, score the exposed surface and cover the sticky surface with a small piece of glass wool. Place the patch in a flask containing sufficient mobile phase to produce a solution containing the equivalent of 0.01% w/v of estradiol, mix with the aid of ultrasound for 10 minutes, shake mechanically for 1 hour and, if necessary, filter through a glass-fibre filter paper (Whatman GF/C is suitable). Using a disposable syringe, collect part of the supernatant liquid and filter through a membrane filter with a pore size of 0.45 µm.
(2) Dilute 1 volume of a 0.1% w/v solution of *estradiol hemihydrate BPCRS* in *acetonitrile* to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but inject 20 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{24}O_2$ in the transdermal patch using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS*.

ASSAY

Use the average of the 10 results obtained in the test for Uniformity of content.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of estradiol per patch.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estradiol Vaginal Tablets

General Notices

Estradiol Vaginal Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Estrogen.

DEFINITION

Estradiol Vaginal Tablets contain Estradiol Hemihydrate. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test for lipophilic solid dosage forms is carried out to demonstrate the appropriate release of estradiol. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The vaginal tablets comply with the requirements stated under Vaginal Preparations and with the following requirements.

Content of estradiol, $C_{18}H_{24}O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of powdered tablets containing the equivalent of 0.38 mg of estradiol, add 50 mL of *propan-2-ol* and allow to disintegrate by stirring overnight. Centrifuge the resulting suspension, evaporate an aliquot of 40 mL of the supernatant to dryness and dissolve the residue in 3 mL of *propan-2-ol*. Evaporate to dryness, reconstitute with 300 µL of *absolute ethanol* to produce a solution containing the equivalent of 0.1% w/v of estradiol, centrifuge and use the supernatant liquid.

(2) 0.1% w/v of *estradiol hemihydrate BPCRS* in *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Kieselgel 60 HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 8 cm.

www.webofpharma.com

https://nhathuocngocanh.com/

(e) After removal of the plate, dry in air and spray with *ethanolic sulfuric acid (5%)*. Heat the plate at 105° for 15 minutes and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

10 volumes of *acetone* and 90 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, size and colour to that in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to estradiol in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of powdered tablets, add *absolute ethanol* to produce a solution containing the equivalent of 0.00024% w/v of estradiol. Stir for a minimum of 16 hours, shake thoroughly, and centrifuge. Evaporate 10 mL of the supernatant to dryness. Dissolve the residue in 1 mL of *water* and add 7 mL of a mixture of 2 volumes of *acetone* and 5 volumes of *toluene*. Mix using a vortex mixer at 12 minute intervals for 1 hour and allow the mixture to stand for 15 minutes before evaporating 5 mL of the organic phase to dryness. Reconstitute the residue in 2 mL of *absolute ethanol* to produce a solution containing the equivalent of 0.00086% w/v of estradiol. Centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with *absolute ethanol*.

(3) 0.0025% w/v of *estradiol hemihydrate BPCRS* and 0.0000125% w/v of *estrone BPCRS* in *absolute ethanol*.

(4) Dilute 1 volume of solution (2) to 10 volumes with *absolute ethanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Water Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A *acetonitrile*.

Mobile phase B *water*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-35	80→15	20→85	linear gradient
35-49	15	85	isocratic
49-50	15→80	85→20	linear gradient
50-55	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to estradiol (retention time about 26 min) are: impurity 2, about 0.7; impurity 3, about 0.96 and estrone, about 1.13.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between estradiol and estrone is at least 7.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) due to impurity 3 and multiply the peak area by the correction factor 0.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 2 is not greater than 1.5 times the area of the peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity 3 is not greater than 1.3 times the area of the peak in the chromatogram obtained with solution (2) (1.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than the equivalent of 2 mg and/or less than 2% w/w of estradiol comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

Solvent A Equal volumes of *acetonitrile R1* and *water*.

(1) Add 7 mL of solvent A to one tablet. Stir the mixture for a minimum of 16 hours with a magnetic stirrer, dilute to 10 mL with the same solvent and centrifuge. Dilute the supernatant liquid with solvent A, if necessary, to produce a solution expected to contain the equivalent of 0.0001% w/v of estradiol.

(2) 0.0001% w/v of *estradiol hemihydrate BPCRS* in solvent A.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.0002% w/v of *estradiol hemihydrate BPCRS* and 0.00007% w/v of *estrone BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Nova-Pak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

(g) When the chromatograms are recorded under the prescribed conditions the retention time of the peak due to estradiol is about 26 minutes.

MOBILE PHASE

450 volumes of *water* and 550 volumes of *acetonitrile R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to estradiol and estrone is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{24}O_2$ in each tablet using the declared content of $C_{18}H_{24}O_2$ in *estradiol hemihydrate BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

Estradiol Vaginal Tablets should be protected from light.

LABELLING

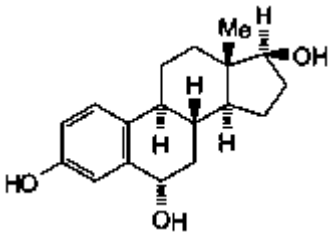
The quantity of active ingredient is stated in terms of the equivalent amount of estradiol.

IMPURITIES

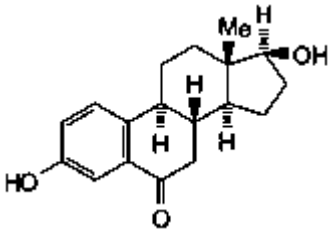
The impurities limited by the requirements of this monograph include those listed under Estradiol Hemihydrate and:

www.webofpharma.com

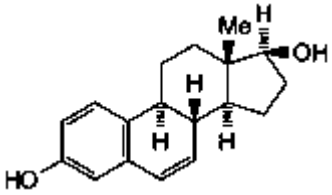
https://thuocngocanh.com/



1. estra-1,3,5(10)-triene-3,6α,17β-triol (6α-hydroxy-estradiol),



2. 3,17β-dihydroxyestra-1,3,5(10)-trien-6-one (6-keto-estradiol),



3. estra-1,3,5(10),6-tetraene-3,17β-diol (Δ6-estradiol).

© Crown Copyright 2022

www.webofpharma.com

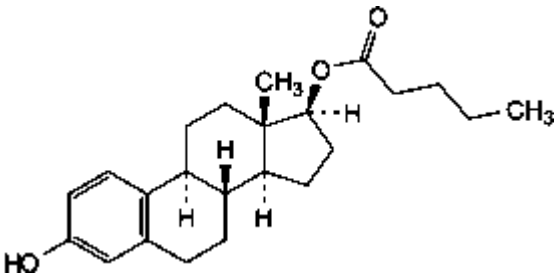
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estradiol Valerate

General Notices

(Ph. Eur. monograph 1614)



$C_{23}H_{32}O_3$ 356.5 *979-32-8*

Action and use

Estrogen.

Ph Eur

DEFINITION

3-Hydroxyestra-1,3,5(10)-trien-17β-yl pentanoate.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *estradiol valerate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

TESTS

Solution S

Dissolve 0.500 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

+ 41 to + 47 (dried substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in *acetonitrile R1* and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 5.0 mL of test solution (a) to 20.0 mL with *acetonitrile R1*.

Reference solution (a) Dissolve 3 mg of *estradiol valerate for system suitability CRS* (containing impurities A, C, D and E) in *acetonitrile R1* and dilute to 1.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *acetonitrile R1*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R1*.

Reference solution (c) Dissolve 50.0 mg of *estradiol valerate CRS* in *acetonitrile R1* and dilute to 10.0 mL with the same solvent. Dilute 5.0 mL of the solution to 20.0 mL with *acetonitrile R1*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped solid core alkylsilyl silica gel for chromatography R* (2.6 µm).

Mobile phase:

— *mobile phase A*: *water R*;

— *mobile phase B*: *acetonitrile R1*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	48	52
1 - 10	48 → 35	52 → 65
10 - 17.5	35 → 0	65 → 100
17.5 - 26	0	100

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 5 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *estradiol valerate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, C, D and E.

Relative retention With reference to estradiol valerate (retention time = about 9 min): impurity A = about 0.1; impurity C = about 0.9; impurity D = about 1.3; impurity E = about 1.7.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to impurity C and estradiol valerate.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity C by 0.5;

— for each impurity, use the concentration of estradiol valerate in reference solution (b).

Limits:

— *impurity D*: maximum 0.4 per cent;

— *impurities A, C*: for each impurity, maximum 0.2 per cent;

— *impurity E*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{23}H_{32}O_3$ taking into account the assigned content of *estradiol valerate CRS*.

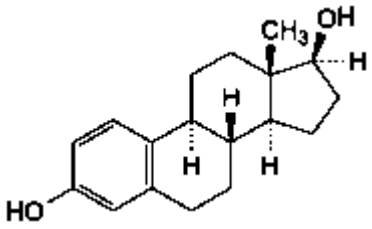
STORAGE

Protected from light.

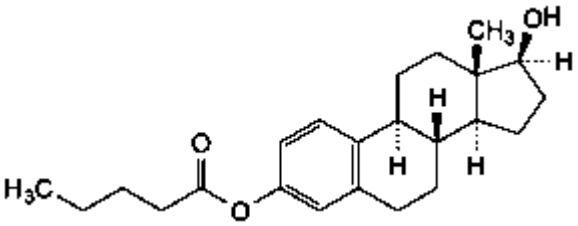
IMPURITIES

Specified impurities *A, C, D, E.*

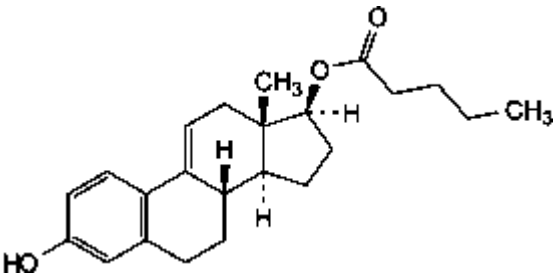
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, F, G, H, I, J.*



A. estra-1,3,5(10)-triene-3,17β-diol (estradiol),



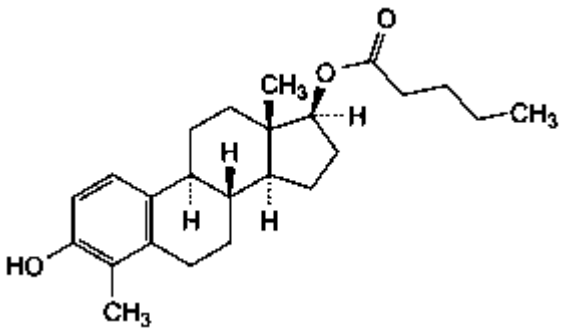
B. 17β-hydroxyestra-1,3,5(10)-trien-3-yl pentanoate,



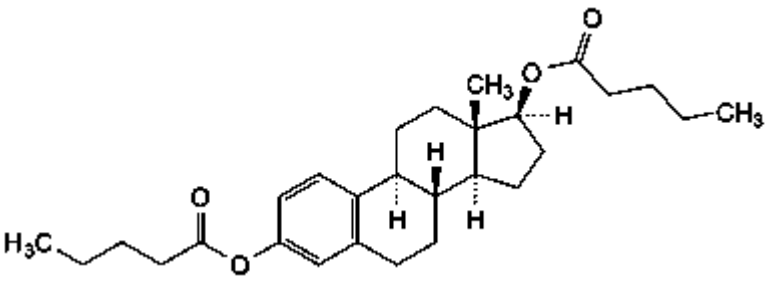
www.webofpharma.com

https://thuocngocanh.com/

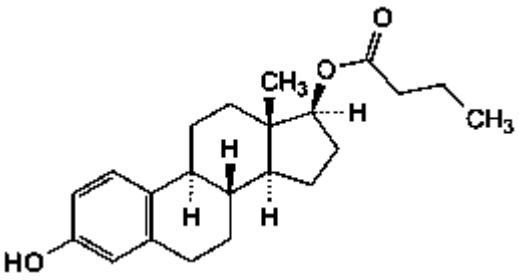
C. 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17β-yl pentanoate,



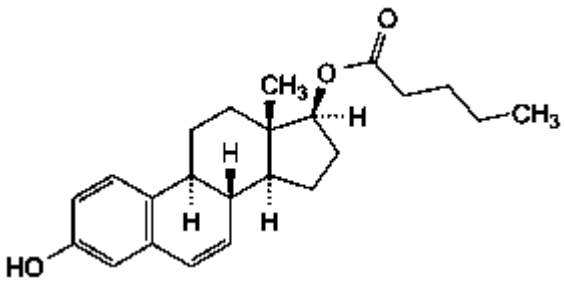
D. 3-hydroxy-4-methylestra-1,3,5(10)-trien-17β-yl pentanoate,



E. estra-1,3,5(10)-trien-3,17β-diyl dipentanoate,



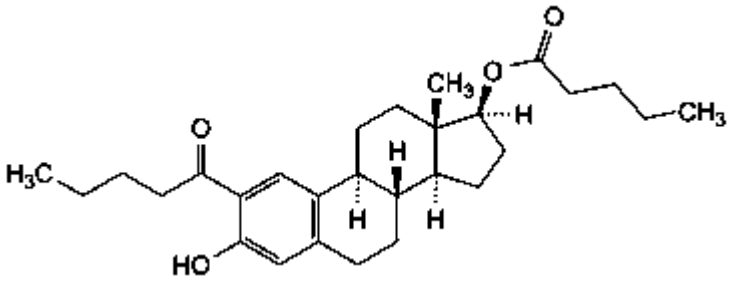
F. 3-hydroxyestra-1,3,5(10)-trien-17β-yl butanoate,



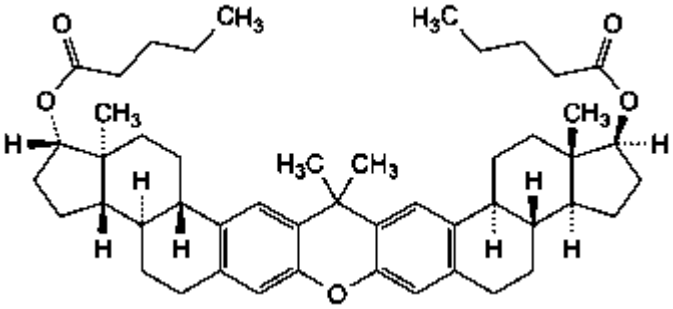
G. 3-hydroxyestra-1,3,5(10),6-tetraen-17β-yl pentanoate,

www.webofpharma.com

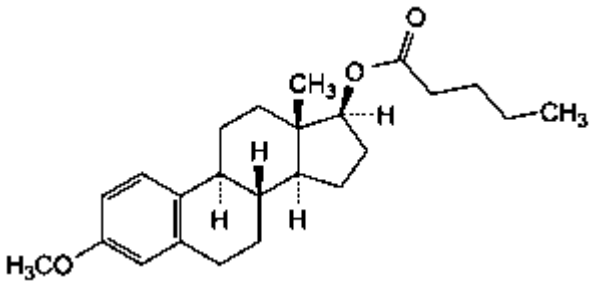
https://thuocngocanh.com/



H. 3-hydroxy-2-pentanoylestra-1,3,5(10)-trien-17β-yl pentanoate,



I. (1*S*,3a*S*,3b*R*,10a*R*,10b*S*,13*S*,13a*S*,15a*S*,18b*S*,20a*S*)-13a,17,17,20a-tetramethyl-2,3,3a,3b,4,5,9,10,10a,10b,11,12,13,13a,14,15,15a,17,18b,19,20,20a-docosahydro-1*H*-bis(cyclopenta[5,6]naphtho)[1,2-*b*:2',1'-*i*]xanthene-1,13-diyl dipentanoate,



J. 3-methoxyestra-1,3,5(10)-trien-17β-yl pentanoate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estramustine Phosphate Capsules

General Notices

Action and use

Cytotoxic alkylating agent.

DEFINITION

Estramustine Phosphate Capsules contain Estramustine Sodium Phosphate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of estramustine phosphate, $C_{23}H_{32}Cl_2NO_6P$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing the equivalent of 0.2 g of Estramustine Phosphate with 10 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of estramustine sodium phosphate *(RS 128)*. In preparing the potassium bromide disc precautions should be taken to exclude moisture and avoid excessive grinding; if necessary heat the prepared disc at 90° for 2 minutes.

B. A 1% w/v solution of the residue obtained in test A yields the reactions characteristic *of sodium salts*, Appendix VI.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of 1 volume of *triethylamine* and 49 volumes of *methanol*.

(1) 4.0% w/v of the residue obtained in test A for Identification.

(2) 0.020% w/v of the residue obtained in test A for Identification.

(3) 0.080% w/v of *17β,17'β-bis{3-[bis(2-chloroethyl)carbamoyloxy]estra1,3,5(10)-trienyl} pyrophosphate BPCRS*.

(4) 0.040% of *estramustine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

www.webofpharma.com

https://thuocngocanh.com/

(e) After removal of the plate, dry in air, spray with *methanolic sulfuric acid (20%)* and heat at 110° for 10 minutes.

MOBILE PHASE

Equal volumes of *butan-2-one*, *propan-2-ol* and *triethylamine hydrogen carbonate solution*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* due to 17β,17′β-bis{3-[bis(2-chloroethyl)carbamoyloxy]estra1,3,5(10)-trienyl} pyrophosphate is not more intense than the corresponding spot in the chromatogram obtained with solution (3) (2%);

any *secondary spot* due to estramustine is not more intense than the corresponding spot in the chromatogram obtained with solution (4) (1%);

Any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Shake a quantity of the mixed contents of 20 capsules containing the equivalent of 0.28 g of Estramustine Phosphate with 20 mL of *water*, dilute to 50 mL with *water* and filter. Dilute 5 mL of the filtrate to 100 mL with *ethanol (50%)* and measure the *absorbance* of the resulting solution at the maximum at 275 nm, Appendix II B. Calculate the content of $C_{23}H_{32}Cl_2NO_6P$ taking 15.4 as the value of A (1%, 1 cm) at the maximum at 275 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of estramustine phosphate.

© Crown Copyright 2022

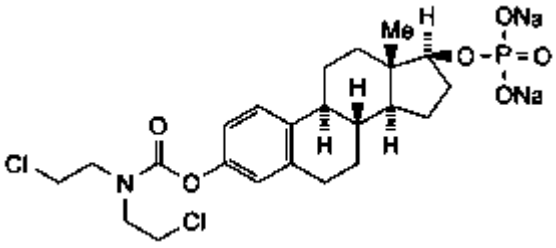
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estramustine Sodium Phosphate

General Notices



$C_{23}H_{30}Cl_2NNa_2O_6P$ 564.4 *52205-73-9*

Action and use

Cytotoxic alkylating agent.

Preparation

Estramustine Phosphate Capsules

DEFINITION

Estramustine Sodium Phosphate is disodium 3-[bis(2-chloroethyl)carbamoyloxy]estra-1,3,5(10)-trien-17β-yl orthophosphate. It contains not less than 97.0% and not more than 103.0% of $C_{23}H_{30}Cl_2NNa_2O_6P$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white or almost white powder.

Freely soluble in *water* and in *methanol*; very slightly soluble in *absolute ethanol*.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of a 0.05% w/v solution exhibits maxima at 267 nm and 275 nm. The *absorbance* at 267 nm is about 0.76 and at 275 nm is about 0.71.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of estramustine sodium phosphate *(RS 128)*. In preparing the potassium bromide disc precautions should be taken to exclude moisture and avoid excessive grinding; if necessary heat the prepared disc at 90° for 2 minutes.

C. A 1% w/v solution yields the reactions characteristic of *sodium salts*, Appendix VI.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Alkalinity

pH of a 0.5% w/v solution, 8.5 to 10.0, Appendix V L.

Clarity and colour of solution

A 5.0% w/v solution is not more opalescent than *reference suspension II*, Appendix IV A, and is *colourless*, Appendix IV B, Method I.

Specific optical rotation

In a 2% w/v solution, +11 to +13, Appendix V F, calculated with reference to the anhydrous substance.

Ionisable chlorine

Dissolve 0.10 g in 10 mL of *water*, add carefully, with mixing, 0.1 mL of a mixture of 10 volumes of *silver nitrate solution* and 1 volume of *nitric acid* and examine immediately. Any opalescence produced is not more intense than that obtained by treating a solution containing 13.4 µg of *sodium chloride* in 10 mL in the same manner (0.1%).

Estradiol 17β-phosphate

Dissolve 50 mg in 5 mL of 0.2M *sodium hydroxide*, add sufficient *ethanol (96%)* to produce 10 mL, mix and immediately measure the *absorbance* at the maxima at 300 nm and 350 nm, Appendix II B. The difference between the two absorbances is not more than 0.34 (1.0%).

Inorganic phosphate

Dissolve 25 mg in 10 mL of *water*, add 4 mL of 1M *sulfuric acid*, 1 mL of a 10% w/v solution of *ammonium molybdate* and 2 mL of *methylaminophenol-sulfite reagent* and allow to stand for 15 minutes. Add sufficient *water* to produce 25 mL, allow to stand for 15 minutes and filter. The *absorbance* of the filtrate at 730 nm, Appendix II B, is not greater than the *absorbance* at 730 nm of a solution obtained by repeating the operation using 10 mL of a 0.00180% w/v solution of *potassium dihydrogen orthophosphate* and beginning at the words ‘add 4 mL of 1M *sulfuric acid*…’.

Volatile matter

Carry out the method for *gas chromatography*, Appendix III B using the following solutions in *water*.

(1) 4.0% w/v of the substance being examined and 0.020% v/v of the internal standard.
(2) 4.0% w/v of the substance being examined.
(3) 0.0040% v/v of *pyridine*, 0.020% v/v of *absolute ethanol* and 0.020% v/v of *butan-1-ol* (internal standard).

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with *acid-washed, silanised diatomaceous support* (80 to 100 mesh) coated with 20% w/w of polyethylene glycol (Carbowax 20M is suitable).
(b) Use *nitrogen* as the carrier gas at 30 mL per minute.
(c) Use isothermal conditions maintained at 120°.
(d) Use an inlet temperature of 200°.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a flame ionisation detector at a temperature of 300°.

(f) Inject 1 µL of each solution.

(g) The peaks elute in the order: ethanol, butan-1-ol, pyridine.

LIMITS

In the chromatogram obtained with solution (1):

the area of the peak due to pyridine is not greater than the area of any corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of any peaks with a retention time less than that of the peak due to the internal standard is not greater than the area of the peak due to ethanol in the chromatogram obtained with solution (3) (0.5%).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in a mixture of 1 volume of *triethylamine* and 49 volumes of *methanol*.

(1) 4.0% w/v of the substance being examined.

(2) 0.020% w/v of the substance being examined.

(3) 0.080% w/v of *17β,17'β-bis{3-[bis(2-chloroethyl)carbamoyloxy]estra1,3,5(10)-trienyl} pyrophosphate BPCRS*.

(4) 0.040% of *estramustine BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *methanolic sulfuric acid (20%)* and heat at 110° for 10 minutes.

MOBILE PHASE

Equal volumes of *butan-2-one*, *propan-2-ol* and *triethylamine hydrogen carbonate solution*.

LIMITS

In the chromatogram obtained with solution (1):

any *secondary spot* due to 17β,17'β-bis{3-[bis(2-chloroethyl)carbamoyloxy]estra1,3,5(10)-trienyl} pyrophosphate is not more intense than the corresponding spot in the chromatogram obtained with solution (3) (2%);

any *secondary spot* due to estramustine is not more intense than the corresponding spot in the chromatogram obtained with solution (4) (1%);

Any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

Water

www.webofpharma.com

https://thuocngocanh.com/

Not more than 5.0% w/w, Appendix IX C. Use 0.2 g.

ASSAY

To 0.5 g add 40 mL of 1M *sodium hydroxide* and boil under a reflux condenser for 60 minutes. Cool and transfer the mixture to a 250 mL graduated flask with the aid of *water*. Add 100 mL of *0.1M silver nitrate VS* and 10 mL of *nitric acid*, dilute to 250 mL with *water* and mix. Filter and titrate the excess of silver nitrate in 50 mL of the filtrate with *0.1M ammonium thiocyanate VS* using 3 mL of *ammonium iron(III) sulfate solution R2* as indicator. Each mL of *0.1M silver nitrate VS* is equivalent to 28.22 mg of $C_{23}H_{30}Cl_2NNa_2O_6P$.

STORAGE

Estramustine Sodium Phosphate should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

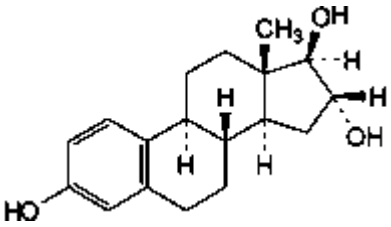
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Estriol

General Notices

(Ph. Eur. monograph 1203)



$C_{18}H_{24}O_3$ 288.4 *50-27-1*

Action and use

Estrogen.

Preparation

Estriol Cream

Ph Eur

DEFINITION

Estra-1,3,5(10)-triene-3,16α,17β-triol.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in dichloromethane.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A, B.

Second identification: C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *estriol CRS*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve 5 mg of *estriol CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *2-propanol R*, *toluene R* (10:90 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Spray with *alcoholic solution of sulfuric acid R*. Heat the plate at 120 °C until the spots clearly develop and allow to cool. Examine in daylight and in ultraviolet light at 366 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 366 nm and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Specific optical rotation (2.2.7)

+ 60 to + 65 (dried substance).

Dissolve 80 mg in *anhydrous ethanol R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *methanol R*, *water R* (50:50 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 25 mL of *methanol R* and dilute to 50.0 mL with *water R*.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *estriol for system suitability CRS* (containing impurities A, D, E and F) in 5 mL of *methanol R* and dilute to 10.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 25.0 mg of *estriol CRS* in 25 mL of *methanol R* and dilute to 50.0 mL with *water R*. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped, charged surface, ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *methanol R1*, *water for chromatography R* (0.01:28:72 *V/V/V*);

— *mobile phase B*: *phosphoric acid R*, *acetonitrile for chromatography R* (0.01:100 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	100	0
9 - 23	100 → 57	0 → 43
23 - 28	57	43

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *estriol for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, D, E and F.

Relative retention With reference to estriol (retention time = about 11 min): impurity A = about 0.95; impurity F = about 1.45; impurity E = about 1.5; impurity D = about 1.8.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 5.0, where H_P = height above the baseline of the peak due to impurity A and H_V = height above the baseline of the lowest point of the curve separating this peak from the peak due to estriol.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.5;

— for each impurity, use the concentration of estriol in reference solution (b).

Limits:

— *impurity F*: maximum 0.5 per cent;

— *impurity E*: maximum 0.3 per cent;

— *impurities A, D*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10
5 - 5.5	90 → 30	10 → 70
5.5 - 7.5	30	70

Injection 5 µL of test solution (b) and reference solutions (a) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to estriol (retention time = about 4 min): impurity A = about 0.9.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (a):

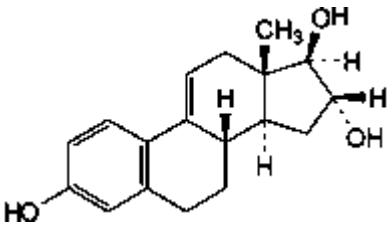
— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to estriol.

Calculate the percentage content of $C_{18}H_{24}O_3$ taking into account the assigned content of *estriol CRS*.

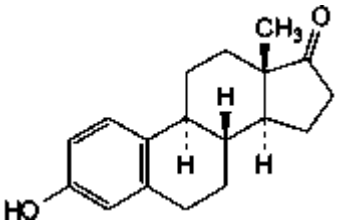
IMPURITIES

Specified impurities *A, D, E, F.*

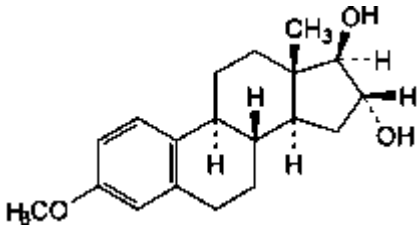
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, G, H, I, J, K.*



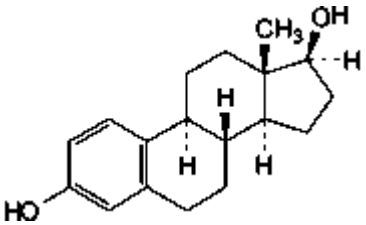
A. estra-1,3,5(10),9(11)-tetraene-3,16α,17β-triol (9,11-didehydroestriol),



B. 3-hydroxyestra-1,3,5(10)-trien-17-one (estrone),



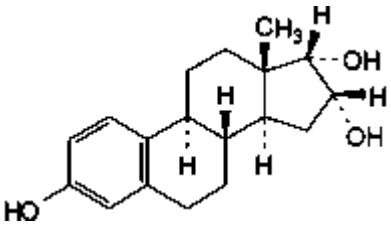
C. 3-methoxyestra-1,3,5(10)-triene-16α,17β-diol (estriol 3-methyl ether),



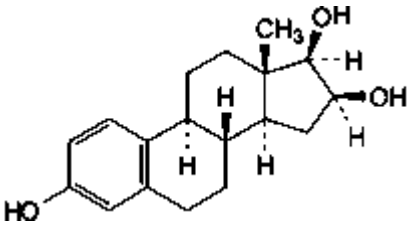
www.webofpharma.com

https://thuocngocanh.com/

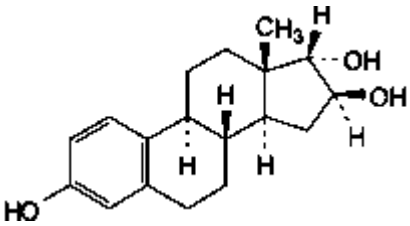
D. estra-1,3,5(10)-triene-3,17β-diol (estradiol),



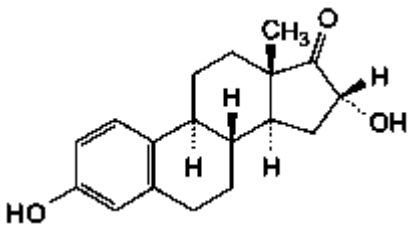
E. estra-1,3,5(10)-triene-3,16α,17α-triol (17-*epi*-estriol),



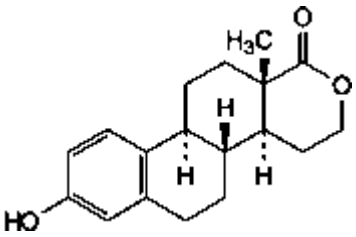
F. estra-1,3,5(10)-triene-3,16β,17β-triol (16-*epi*-estriol),



G. estra-1,3,5(10)-triene-3,16β,17α-triol (16,17-*epi*-estriol),



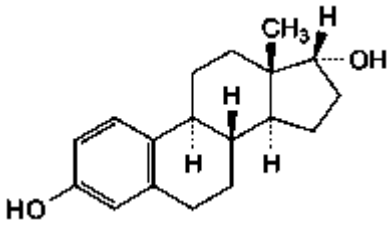
H. 3,16α-dihydroxyestra-1,3,5(10)-trien-17-one,



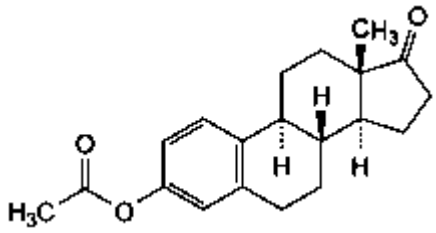
I. 3-hydroxy-17-oxa-17a-homoestra-1,3,5(10)-trien-17a-one,

www.webofpharma.com

https://thuvienthuocngocanh.com/



J. estra-1,3,5(10)-triene-3,17α-diol (17-*epi*-estradiol),



K. 17-oxoestra-1,3,5(10)-trien-3-yl acetate (estrone acetate).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Estriol Cream

General Notices

Action and use

Estrogen.

DEFINITION

Estriol Cream contains Estriol in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of estriol, $C_{18}H_{24}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) To a quantity of cream containing 2 mg of Estriol add 50 mL of solvent, heat on a water bath and mix until the cream has completely dispersed, cool the contents in ice, centrifuge and use the supernatant liquid.

(2) 0.004% w/v of *estriol BPCRS*.

(3) 0.004% w/v each of *estriol BPCRS* and *prednisolone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel 60 high performance precoated plate (Merck HPTLC silica gel 60 is suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry the plate in a horizontal position at 100 to 105°. Dilute 2 mL of *sulfuric acid* to 100 mL with *ethanol (96%)* and spray the solution evenly onto the plate. Examine the plate in daylight.

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

www.webofpharma.com

https://nhathuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.5 to 4.5, Appendix V L.

Disperse 10 g of the cream in 10 mL of *water*, with continuous stirring throughout the pH determination.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

(1) To a quantity of cream containing 0.5 mg of Estriol add 20 mL of solvent, heat on a water bath and mix until the cream has completely dissolved, allow to cool to room temperature and add sufficient solvent to produce 25 mL. Cool the contents in ice for 15 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 5 volumes of solution (1) to 100 volumes, further dilute 10 volumes of this solution to 100 volumes.

(3) Dilute 10 volumes of solution (2) to 100 volumes.

(4) 0.01% w/v of *estriol impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 280 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

5 volumes of *methanol*, 38 volumes of *acetonitrile* and 57 volumes of *water*.

For solutions (3) and (4), when the chromatograms are recorded under the prescribed conditions, the retention times for estriol and 16-epi-estriol are about 5 minutes and about 7 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, (a) in the chromatogram obtained with solution (4), the *resolution factor* between the peaks due to estriol and 16-epi-estriol is at least 2.5 and (b) in the chromatogram obtained with solution (3) the *signal-to-noise ratio* of the principal peak is at least 10.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than twice the principal peak in the chromatogram obtained with solution (2) (1%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

(1) To a quantity of cream containing 0.5 mg of Estriol add 20 mL of *methanol*, heat on a water bath and mix until the cream has completely dispersed, allow to cool to room temperature and add sufficient *methanol* to produce 25 mL, transfer to a centrifuge tube and cool the contents in ice for 15 minutes, centrifuge and dilute 5 volumes of the supernatant liquid to 100 volumes with *methanol*.

(2) 0.0001% w/v of *estriol BPCRS*.

(3) 0.01% w/v of *estriol impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to estriol and 16-epi-estriol is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{24}O_3$ in the cream using the declared content of $C_{18}H_{24}O_3$ in *estriol BPCRS*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

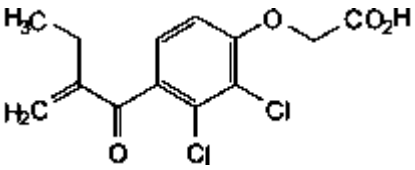
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Etacrynic Acid

General Notices

(Ph. Eur. monograph 0457)



$C_{13}H_{12}Cl_2O_4$ 303.1 *58-54-8*

Action and use

Loop diuretic.

Ph Eur

DEFINITION

[2,3-Dichloro-4-(2-methylenebutanoyl)phenoxy]acetic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in ethanol (96 per cent). It dissolves in ammonia and in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: C.

Second identification: A, B, D, E.

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 121 °C to 124 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Solvent mixture 103 g/L solution of *hydrochloric acid R*, *methanol R* (1:99 *V/V*).

Test solution Dissolve 50.0 mg in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 100.0 mL with the solvent mixture.

Spectral range 230-350 nm.

Absorption maximum 270 nm.

Shoulder About 285 nm.

Specific absorbance at the absorption maximum 110 to 120.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *etacrynic acid CRS*.

D. Dissolve about 30 mg in 2 mL of *aldehyde-free alcohol R*. Dissolve 70 mg of *hydroxylamine hydrochloride R* in 0.1 mL of *water R*, add 7 mL of *alcoholic potassium hydroxide solution R* and dilute to 10 mL with *aldehyde-free alcohol R*. Allow to stand and add 1 mL of the supernatant to the solution of the substance to be examined. Heat the mixture on a water-bath for 3 min. After cooling, add 3 mL of *water R* and 0.15 mL of *hydrochloric acid R*. Examined in ultraviolet light at 254 nm, the mixture shows an intense blue fluorescence.

E. Dissolve about 25 mg in 2 mL of a 42 g/L solution of *sodium hydroxide R* and heat in a water-bath for 5 min. Cool and add 0.25 mL of a mixture of equal volumes of *sulfuric acid R* and *water R*. Add 0.5 mL of a 100 g/L solution of *chromotropic acid, sodium salt R* and, carefully, 2 mL of *sulfuric acid R*. An intense violet colour is produced.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* (40:60 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *etacrynic acid for system suitability CRS* (containing impurities A, B and C) in 5 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: 1 per cent *V/V* solution of *triethylamine R* adjusted to pH 6.8 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.5	70	30
2.5 - 3	70 → 65	30 → 35
3 - 6	65	35
6 - 7	65 → 45	35 → 55
7 - 22	45	55

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *etacrynic acid for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C.

Relative retention With reference to etacrynic acid (retention time = about 9 min): impurity A = about 0.8; impurity B = about 1.3; impurity C = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to impurity A and etacrynic acid.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity B = 0.6; impurity C = 1.3;

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities A, B*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 2.000 g by drying *in vacuo* at 60 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

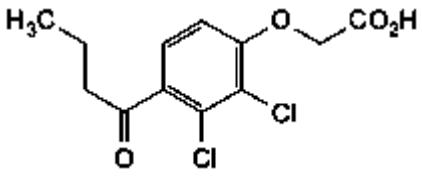
ASSAY

Dissolve 0.250 g in 100 mL of *methanol R* and add 5 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

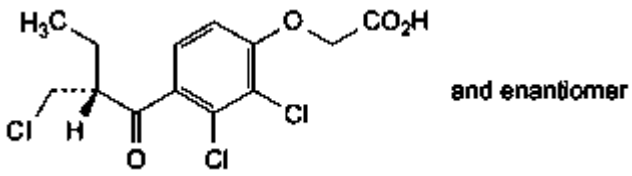
1 mL of *0.1 M sodium hydroxide* is equivalent to 30.31 mg of $C_{13}H_{12}Cl_2O_4$.

IMPURITIES

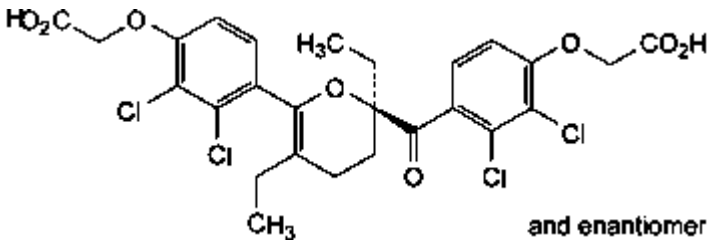
Specified impurities *A, B, C.*



A. (4-butanoyl-2,3-dichlorophenoxy)acetic acid,



B. [2,3-dichloro-4-[2-(chloromethyl)butanoyl]phenoxy]acetic acid,



www.webofpharma.com

https://thuocngocanh.com/

C. [4-[2-[4-(carboxymethoxy)-2,3-dichlorobenzoyl]-2,5-diethyl-3,4-dihydro-2*H*-pyran-6-yl]-2,3-dichlorophenoxy]acetic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

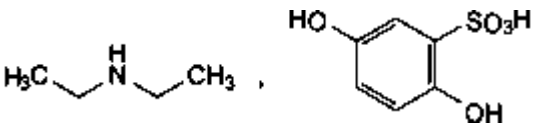
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Etamsylate

General Notices

(Ph. Eur. monograph 1204)



$C_{10}H_{17}NO_5S$ 263.3 *2624-44-4*

Action and use

Antifibrinolytic.

Ph Eur

DEFINITION

N-Ethylethanamine 2,5-dihydroxybenzenesulfonate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in methanol, soluble in anhydrous ethanol, practically insoluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 127 °C to 134 °C.

www.webofpharma.com

https://thuocngocanh.com/

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *etamsylate CRS*.

C. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.100 g in *water R* and dilute to 200.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *water R*. Examine immediately.

Spectral range 210-350 nm.

Absorption maxima At 221 nm and 301 nm.

Specific absorbance at the absorption maximum at 301 nm 145 to 151.

D. Into a test-tube, introduce 2 mL of freshly prepared solution S (see Tests) and 0.5 g of *sodium hydroxide R*. Warm the mixture and place a wet strip of *red litmus paper R* near the open end of the tube. The colour of the paper becomes blue.

TESTS

Solution S

Dissolve 10.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S, when freshly prepared, is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

4.5 to 5.6 for solution S.

Related substances

Liquid chromatography (2.2.29). *Keep all solutions at 2-8 °C.*

Buffer solution Dissolve 1.2 g of *anhydrous sodium dihydrogen phosphate R* in 900 mL of *water for chromatography R*. Adjust to pH 6.5 with *disodium hydrogen phosphate solution R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 10 mg of the substance to be examined and 10 mg of *hydroquinone R* (impurity A) in *water R* and dilute to 10 mL with the same solvent. Dilute 1 mL of the solution to 100 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase:* spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R1*, buffer solution (10:90 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL.

Run time 11 times the retention time of etamsylate.

Relative retention With reference to etamsylate (retention time = about 6 min): impurity A = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 8.0 between the peaks due to etamsylate and impurity A.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.5;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Iron (*2.4.9*)

Maximum 10 ppm, determined on solution S.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* in an oven at 60 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in a mixture of 10 mL of *water R* and 40 mL of *dilute sulfuric acid R*. Titrate with *0.1 M cerium sulfate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M cerium sulfate* is equivalent to 13.16 mg of $C_{10}H_{17}NO_5S$.

www.webofpharma.com

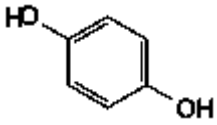
https://thuocngocanh.com/

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A.*



A. benzene-1,4-diol (hydroquinone).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

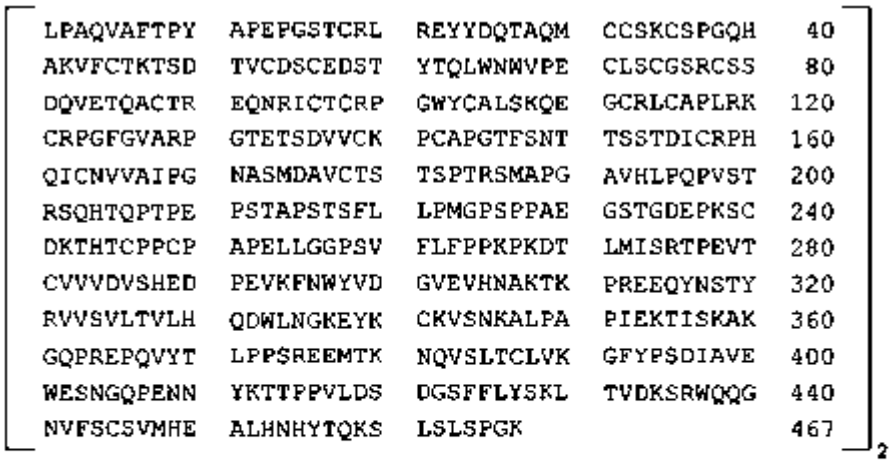
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Etanercept

General Notices

(Ph. Eur. monograph 2895)



disulfide bridges (the list is not exhaustive):
240-240′, 246-246′, 249-249′, 281-341, 387-445, 281′-341′, 387′-445′

***N*-glycosylation sites:**
149, 171, 317, 149′, 171′, 317′

predominant *O*-glycosylation sites:
184, 199, 200, 205, 208, 212, 213, 216, 217, 226, 184′, 199′, 200′, 205′, 208′, 212′, 213′, 216′, 217′, 226′

$C_{2224}H_{3472}N_{618}O_{701}S_{36}$ (monomer) *185243-69-0*

M_r approx. 51 200 (monomer without glycosylation)

Action and use

Human tumour necrosis factor receptor fusion protein; treatment of rheumatoid arthritis and psoriasis.

Ph Eur

DEFINITION

Dimeric fusion protein consisting of the extracellular ligand-binding portion of the human tumour necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the CH2 domain, the CH3 domain and the hinge region, but not the CH1 domain of IgG1. Etanercept consists of 934 amino acids and has an apparent molecular mass of approximately 150 kDa.

www.webofpharma.com

https://thuocngocanh.com/

Etanercept represents a glycosylated protein with multiple *N*- and *O*-linked glycosylation sites. It shows full occupancy of *N*-linked glycans at N149, N171 and N317.

It contains one or more suitable buffering and/or stabilising agents.

Content (milligrams of protein per millilitre) As approved by the competent authority.

Potency

1.3×10^6 to 3.6×10^6 IU per milligram of protein.

PRODUCTION

Etanercept is produced in a suitable mammalian cell expression system by a method based on recombinant DNA (rDNA) technology. In the course of product development, it must be demonstrated that the manufacturing process consistently produces a product with the expected *O*-glycan occupancy using a suitably qualified assay.

Prior to release, the following tests are carried out on each batch of etanercept, unless exemption has been granted by the competent authority.

Host-cell-derived proteins

The limit is approved by the competent authority.

Host-cell and vector-derived DNA

The limit is approved by the competent authority.

N-Glycan analysis

Use a suitable procedure developed according to general chapter *2.2.59. Glycan analysis of glycoproteins*, section 2-3:

— release the glycans using one of the agents described in Table 2.2.59.-1, for example peptide *N*-glycosidase F (PNGase F);

— label the released glycans with one of the fluorescent labelling agents described in Table 2.2.59.-2, for example 2-aminobenzamide;

— analyse the labelled glycans by liquid chromatography (*2.2.29*) using fluorescence detection.

The following procedure is given as an example.

Test solution To 4 µL of the preparation to be examined (about 25 mg/mL) add 21 µL of *water R*, 3 µL of *0.25 M sodium phosphate buffer solution pH 7.5 R* and 2 µL of a 500 000 U/mL solution of *peptide N-glycosidase F R*. Mix and incubate at 37 °C for 20-24 h. Label the released glycans with 2-aminobenzamide using a suitable procedure. The procedure employs a combination of reagents optimised and validated for the efficient labelling of glycans, and for the subsequent extraction and recovery of the labelled glycans from the reaction. Resuspend or dilute the labelled glycans in 100 µL of *water R*.

Reference solution (a) Dissolve the contents of a vial of *etanercept CRS* in *water R* to obtain a concentration of about 25 mg/mL. Carry out the release and labelling of glycans in the same manner as for the test solution. Resuspend or dilute the labelled glycans in 100 µL of

www.webofpharma.com

https://thuocngocanh.com/

water R.

Reference solution (b) Use a suitable etanercept in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate consistency of production. Dilute, if necessary, with *water R* to obtain a concentration of about 25 mg/mL. Carry out the release and labelling of glycans in the same manner as for the test solution. Resuspend or dilute the labelled glycans in 100 µL of *water R*.

Blank solution Prepare at the same time and in the same manner as for the test solution but using *water R* instead of the preparation to be examined.

Analyse the labelled glycans by liquid chromatography (*2.2.29*).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *carbamoylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 9.8 mL of *formic acid R* and 500 mL of *water for chromatography R*, adjust to pH 4.0 with *ammonia R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	20 → 30	80 → 70
2 - 67.0	30 → 52	70 → 48
67.0 - 67.1	52 → 80	48 → 20
67.1 - 73.0	80	20

Flow rate 0.4 mL/min.

Detection Fluorimeter at 330 nm for excitation and 420 nm for emission.

Autosampler Set at 2-8 °C.

Injection 10 µL.

Identification of peaks Use the chromatogram shown in Figure 2895.-1 to identify the 2 groups of oligosaccharides corresponding to neutral (peaks 1 to 5) and sialylated (peaks 6 to 9) *N*-glycans; record the retention time of each peak in both groups.

www.webofpharma.com

https://thuocngocanh.com/

System suitability:

— the chromatogram obtained with reference solution (a) is qualitatively similar to the chromatogram supplied with *etanercept CRS* and peaks 1 to 9 are clearly visible;

— no significant peaks are observed in the chromatogram obtained with the blank solution.

Results:

— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (b);

— the retention times of the peaks in the chromatogram obtained with the test solution correspond to those in the chromatogram obtained with reference solution (b);

— no additional peaks are observed in the chromatogram obtained with the test solution in comparison with the chromatogram obtained with reference solution (b).

Calculate the relative peak areas of the individual peaks corresponding to neutral and sialylated *N*-glycans with reference to the sum of the areas of all retained glycan peaks.

Calculate the percentage contents of the neutral and sialylated groups, using the following expressions:

$$\frac{A}{A+B} \times 100$$

$$\frac{B}{A+B} \times 100$$

A	=	sum of the areas of the peaks due to neutral *N*-glycans;
B	=	sum of the areas of the peaks due to sialylated *N*-glycans.

NOTE: peaks 2 and 3 are separate peaks, but they are integrated together.

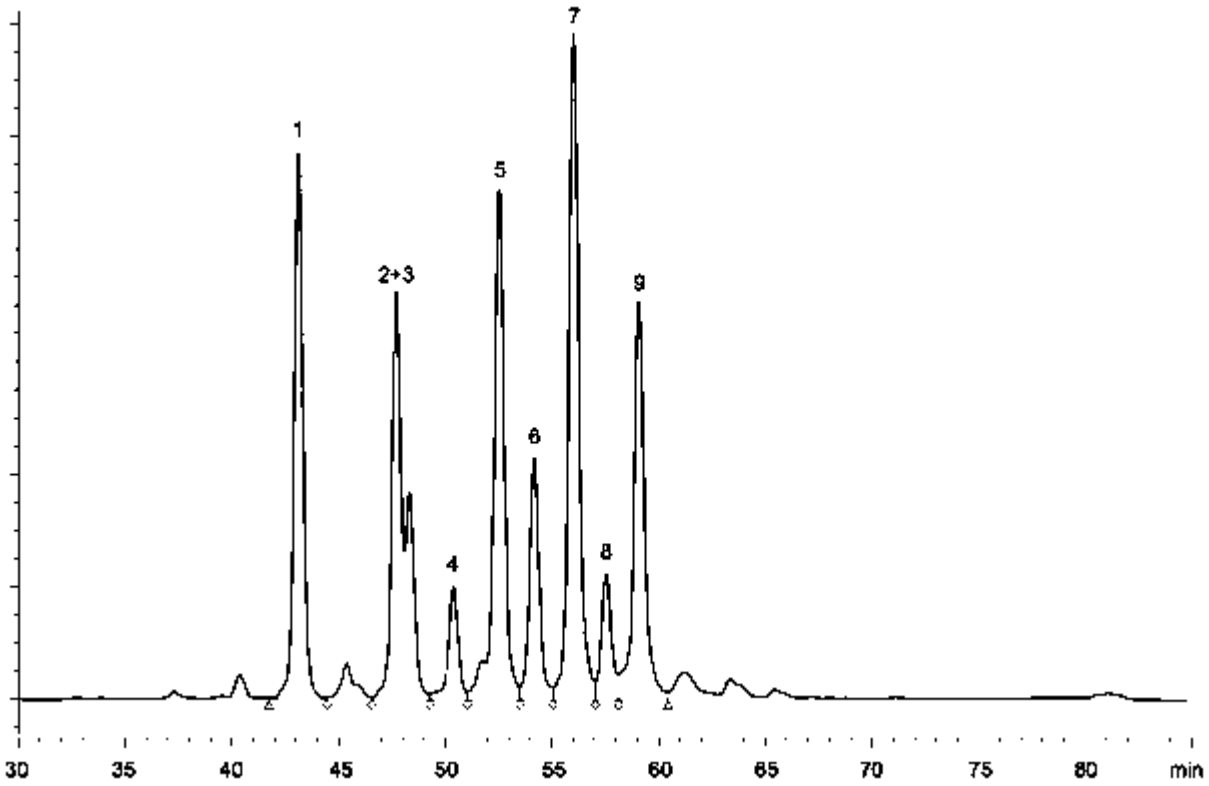
Limits:

— *percentage of neutral N-glycans*: as approved by the competent authority;

— *percentage of sialylated N-glycans*: as approved by the competent authority.

www.webofpharma.com

https://thuocngocanh.com/



Peak	Charged	Structure	Peak	Charged	Structure	Peak	Charged	Structure	Peak	Charged	Structure
1.	No	Asialo-, agalacto-, biantennary, core-fucosylated	4.	No	Asialo-, galactosylated biantennary	6.	Yes	Monosialylated-, galactosylated biantennary	8.	Yes	Disialylated, galactosylated biantennary
2+3.	No	Asialo-, mono-galactosylated biantennary, core-fucosylated	5.	No	Asialo-, galactosylated biantennary, core-fucosylated	7.	Yes	Monosialylated-, galactosylated biantennary, core-fucosylated	9.	Yes	Disialylated-, galactosylated biantennary, core-fucosylated

Figure 2895.-1. – *Chromatogram for N-glycan analysis of etanercept*

CHARACTERS

Appearance

Clear, almost colourless, slightly yellow or slightly brown liquid.

IDENTIFICATION

A. It complies with the limits of the assay (potency).

B. Peptide mapping (*2.2.55*).

www.webofpharma.com

https://thuocngocanh.com/

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of about 15 mg/mL.

Reference solution Dissolve the contents of a vial of *etanercept CRS* in *water R* to obtain a concentration of about 15 mg/mL.

Reduction and alkylation To 200 µL of the test solution add 500 µL of *guanidine-tris(hydroxymethyl)aminomethane buffer solution pH 8.3 R* and 7 µL of a 154 g/L solution of *dithiothreitol R*. Mix and incubate at 65 °C for 15 min. Cool in an ice-bath for 5-10 min, then add 15.4 µL of a freshly prepared 185 g/L solution of *iodoacetamide R*. Mix and allow to stand protected from light for 10 min. Add 1.4 µL of a 154 g/L solution of *dithiothreitol R*. Mix and allow to stand protected from light for 10 min.

Digestion To 97 µL of the reduced test solution prepared previously, add 903 µL of *0.1 M tris-hydrochloride buffer solution pH 7.5 R*. Add 9.6 µL of a 500 000 U/mL solution of *peptide N-glycosidase F R* and incubate at 37 °C for 1 h. Add 40 µL of a 1 mg/mL solution of *trypsin for peptide mapping R* and incubate at 37 °C for 5 h. Heat at 95 °C for 5 min and cool in ice for 5 min. Adjust to pH 2 with about 30 µL of a 150 g/L solution of *trifluoroacetic acid R*.

Carry out the reduction/alkylation and digestion steps for the reference solution in the same manner as for the test solution.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (*2.2.29*).

Column:

— *size*: *l* = 0.25 m, Ø = 3.2 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm;

— *temperature*: 30-35 °C.

Mobile phase:

— *mobile phase A*: mix 3 g of *trifluoroacetic acid R* and 2000 mL of *water for chromatography R*;

— *mobile phase B*: mix 2 g of *trifluoroacetic acid R*, 330 mL of *water for chromatography R* and 1320 mL of *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	98	2
5 - 125	98 → 50	2 → 50
125 - 140	50 → 5	50 → 95

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 220 nm.

www.webofpharma.com

https://nhathuocngocanh.com/

Autosampler Set at 2-8 °C.

Injection 200 µL.

System suitability:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram supplied with *etanercept CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

TESTS

pH (*2.2.3*)

As approved by the competent authority.

Sialic acid

Use a suitable procedure developed according to general chapter *2.2.59*. *Glycan analysis of glycoproteins*, section 2-4:

— release the sialic acid by acid hydrolysis pre-treatment of the preparation to be examined;

— label the released sialic acid with a fluorescent labelling reagent, for example 1,2-diamino-4,5-methylenedioxybenzene, using a suitable procedure;

— analyse the labelled sialic acid by liquid chromatography (*2.2.29*) using fluorescence detection.

Solution A Dissolve 8.71 g of *arginine R* in 40 mL of *water R*. Add 0.5 mL of a 10 g/L solution of *polysorbate 80 R*, mix and adjust to pH 7.3 with *phosphoric acid R*. Dilute to 250 mL with *water R*.

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of about 5 mg/mL. Further dilute with solution A to obtain a concentration of about 1 mg/mL. To 50 µL of this solution add 50 µL of a 480 g/L solution of *glacial acetic acid R* and incubate at 90 °C for 65 min. Cool, briefly centrifuge and evaporate to dryness. Label the released sialic acid using a suitable procedure; for example, add 15 µL of a 1.6 g/L solution of *1,2-diamino-4,5-methylenedioxybenzene dihydrochloride R* containing 78.1 g/L of *2-mercaptoethanol R* and 3.1 g/L of *sodium dithionite R* and incubate at 50 °C for 3 h. Dilute to 1 mL with *water R*.

Reference solution (a) Dissolve the contents of a vial of *etanercept CRS* in *water R* to obtain a concentration of about 5 mg/mL. Carry out the release and labelling of sialic acid in the same manner as for the test solution. Dilute to 1 mL with *water R*.

Reference solution (b) Dissolve *N-acetylneuraminic acid R* in *water R* to obtain a concentration of about 1 mg/mL. Mix 40 µL of the solution, 40 µL of a 1 mg/mL solution of *bovine albumin R1* and 120 µL of solution A. Use 50 µL of this solution to carry out the release and labelling of sialic acid in the same manner as for the test solution. Dilute with *water R* to obtain a concentration of 0.01 µg/µL.

Standard solutions Dilute reference solution (b) with *water R* to prepare a standard curve with concentrations in the range of 1.25-7.50 ng/µL (6 concentrations, typically 1.25 ng/µL, 2.50 ng/µL, 3.75 ng/µL, 5.00 ng/µL, 6.25 ng/µL and 7.50 ng/µL). Analyse the labelled sialic acid by liquid chromatography (*2.2.29*).

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 8 nm;

— *temperature*: 35 °C.

Mobile phase Mix 8 mL of *acetonitrile R*, 500 mL of *methanol R* and 1820 mL of *water for chromatography R*; mix thoroughly.

Flow rate 1 mL/min.

Detection Fluorimeter at 374 nm for excitation and 448 nm for emission.

Autosampler Set at 2-8 °C.

Injection 20 µL.

Retention time Sialic acid = about 10.5 min.

Calculate the sialic acid content in the preparation to be examined using the standard curve and the content of sialic acid (*N*-acetylneuraminic acid) in the standard solutions. Report the molar ratio (number of moles of sialic acid per mole of etanercept), using the molar mass of the monomer.

System suitability:

— the peak due to sialic acid in the chromatogram obtained with reference solution (a) is visible and is similar to the corresponding peak in the chromatogram supplied with *etanercept CRS*;

— *repeatability*: maximum relative standard deviation of 15 per cent for the sialic acid content expressed as the molar ratio, determined on 3 consecutive injections of reference solution (a);

— the coefficient of determination (R^2) calculated for the standard curve is not less than 0.9995.

Results:

— the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (a).

Limit:

— 8 to 19 moles of sialic acid per mole of etanercept.

Related proteins

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of about 2 mg/mL.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution Dissolve the contents of a vial of *etanercept CRS* in *water R* to obtain a concentration of about 2 mg/mL.

Column:

— *size*: *l* = 0.035 m, Ø = 4.6 mm;

— *stationary phase*: *butylated polymethacrylate gel R* (2.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: dissolve 28.4 g of *anhydrous disodium hydrogen phosphate R* and 475.9 g of *ammonium sulfate R* in *water for chromatography R* and dilute to 1950 mL with the same solvent; adjust to pH 7.0 with *phosphoric acid R* and dilute to 2000 mL with *water for chromatography R*;

— *mobile phase B*: dissolve 28.4 g of *anhydrous disodium hydrogen phosphate R* in *water for chromatography R* and dilute to 1950 mL with the same solvent; adjust to pH 7.0 with *phosphoric acid R* and dilute to 2000 mL with *water for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 50	100 → 0	0 → 100

Flow rate 1.0 mL/min.

Detection Fluorimeter at 278 nm for excitation and 350 nm for emission.

Autosampler Set at 10 °C.

Injection 5 µL; perform 3 injections.

Relative retention With reference to etanercept (retention time = about 28.5 min): peak 1 = 0.96; peak 3 = 1.12.

System suitability Reference solution:

— the chromatogram obtained is qualitatively similar to the chromatogram supplied with *etanercept CRS*;

— peaks 1 and 3 are clearly separated from the peak due to etanercept.

Results:

— no additional peaks are observed in the chromatogram obtained with the test solution in comparison with the chromatogram obtained with the reference solution.

Limits:

— *peak 1*: maximum 5 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *peak 3*: maximum 28 per cent;

— *sum of all peaks other than the principal peak*: maximum 30 per cent.

Impurities with molecular masses greater than that of etanercept

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Solution A Dissolve 8.8 g of *sodium chloride R* and 15.6 g of *sodium dihydrogen phosphate R* in 900 mL of *water for chromatography R* and dilute to 1000 mL with the same solvent.

Solution B Dissolve 8.75 g of *sodium chloride R* and 14.2 g of *anhydrous disodium hydrogen phosphate R* in 900 mL of *water for chromatography R* and dilute to 1000 mL with the same solvent.

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 2.5 mg/mL.

Reference solution Dissolve the contents of a vial of *etanercept CRS* in *water R* to obtain a concentration of 2.5 mg/mL.

Column:

— *size*: *l* = 0.30 m, Ø = 8.0 mm;

— *stationary phase*: *hydroxypropylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm and of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 10 000 to 1000 000.

Mobile phase Mix 220 mL of solution A and 780 mL of solution B, and adjust to pH 7.2 with solution A or solution B.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Autosampler Set at 2-8 °C.

Injection 14 µL; perform at least 3 injections.

Relative retention With reference to etanercept monomer (retention time = about 7.8 min): aggregates = 0.84; high molecular mass species = 0.89.

Any shoulder appearing on the descending part of the peak due to etanercept monomer is included in its area.

System suitability Reference solution:

— the chromatogram obtained is qualitatively similar to the chromatogram supplied with *etanercept CRS*;

— *resolution*: minimum 1.5 between the peaks due to the high molecular mass species and etanercept monomer;

— *number of theoretical plates*: minimum 3000 calculated for the peak due to etanercept monomer.

Limit:

www.webofpharma.com

https://thuocngocanh.com/

— *sum of the peaks eluted before the principal peak*: maximum 8.0 per cent.

Impurities with molecular masses differing from that of etanercept

Polyacrylamide gel electrophoresis (2.2.31) under both reducing and non-reducing conditions.

Gel dimensions 1.0 mm thick.

Resolving gel 8-16 per cent acrylamide.

Sample buffer (non-reducing conditions) *concentrated SDS-PAGE sample buffer R*.

Sample buffer (reducing conditions) *concentrated SDS-PAGE sample buffer for reducing conditions R*.

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 0.2 mg/mL. Mix 1 volume of this solution and 1 volume of sample buffer.

Reference solution (a) Dissolve the contents of a vial of *etanercept CRS* in *water R* to obtain a concentration of 0.2 mg/mL. Mix 1 volume of the solution and 1 volume of sample buffer.

Reference solution (b) 0.01 mg/mL solution of *bovine albumin R*.

Reference solution (c) Mix 1 volume of reference solution (b) and 4 volumes of *concentrated SDS-PAGE sample buffer R*.

Reference solution (d) Mix 1 volume of reference solution (b) and 19 volumes of *concentrated SDS-PAGE sample buffer R*.

Reference solution (e) A solution of molecular mass markers suitable for calibrating SDS-polyacrylamide gels in the range of 5-200 kDa.

Sample treatment Heat at 90-105 °C for 5 min and load onto the gel within 15 min.

Application 10 µL.

Detection By silver staining.

Identification of bands:

— *non-reducing conditions*: the band corresponding to etanercept of an apparent molecular mass of approximately 150 kDa is present; related protein bands with apparent molecular masses of approximately 60 kDa, 100 kDa, 120 kDa, 225 kDa, 250 kDa may also be present;

— *reducing conditions*: the band corresponding to etanercept of an apparent molecular mass of approximately 76 kDa is present; related protein bands with apparent molecular masses of approximately 25 kDa, 35 kDa, 55 kDa, 200 kDa may also be present.

System suitability:

— the bands in the electropherogram obtained with reference solution (a) are clearly visible;

— the band in the electropherogram obtained with reference solutions (b), (c) and (d) is clearly visible;

— all expected bands in the electropherogram obtained with reference solution (e) are visible and clearly separated.

www.webofpharma.com

https://thuocngocanh.com/

Results:

— the electropherogram obtained with the test solution is similar to the electropherogram obtained with reference solution (a);

— the electropherogram obtained with the test solution shows no additional band that is more intense than that of the band in the electropherogram obtained with reference solution (d).

Microbiological contamination (2.6.12)

Maximum 1 CFU/mL.

ASSAY

Protein (2.5.33, Method 1)

Test solution Dilute the preparation to be examined gravimetrically with a suitable buffer to obtain a concentration of 1.0 mg/mL. Prepare in triplicate.

Reference solution Dissolve the contents of a vial of *etanercept CRS* in a suitable buffer to obtain a concentration of 1.0 mg/mL.

Record the absorbance spectrum between 250 nm and 400 nm. Measure the value at the absorbance maximum of 280 nm after correction for any light scattering measured up to 320 nm. Calculate the protein concentration of etanercept taking into account the assigned content of *etanercept CRS*.

Potency

The potency of etanercept is determined by comparison of dilutions of the test preparation with the dilutions of *etanercept BRP* using a suitable cell-based assay based on the inhibitory action of etanercept on the biological activity of TNF-α and a suitable readout for assessing this inhibitory effect.

The following procedure is given as an example.

U937 apoptosis assay (2.7.26, Procedure A)

Carry out the assay as described with the following modifications.

Test solution Dilute the preparation to be examined with assay medium to obtain a concentration of about 21 ng/mL. Use this solution to prepare 10 additional test sample dilutions (a dilution step of 1.4 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

Reference solution Reconstitute the contents of 1 vial of *etanercept BRP* with sterilised *water for injections R* to obtain a concentration of 10 000 IU/mL. Further dilute with assay medium to obtain a concentration of 42 IU/mL. Use this solution to prepare 10 additional reference sample dilutions on a dilution plate to generate the standard curve (a dilution step of 1.4 has been found suitable). Analyse 2 independent dilutions per plate.

Result The estimated potency is not less than 80 per cent and not more than 140 per cent relative to the reference solution. The confidence limits (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the estimated potency.

www.webofpharma.com

https://thuocngocanh.com/

In addition, the following procedures have been found suitable:

WEHI-164 cytotoxicity assay (*2.7.26, Procedure B*)

Carry out the assay as described with the following modifications.

Test solution Dilute the preparation to be examined with assay medium to obtain a concentration of about 96 ng/mL. Analyse 2 independent dilutions per plate.

Reference solution Reconstitute the contents of 1 vial of *etanercept BRP* with sterilised *water for injections R* to obtain a concentration of 10 000 IU/mL. Further dilute with assay medium to obtain a concentration of 192 IU/mL. Analyse 2 independent dilutions per plate.

Plate preparation Add 300 µL of the test or reference solutions (column 2, rows A-H). Further prepare a series of 1.5-fold dilutions (columns 3-12, rows A-H), by removing 200 µL from column 2 and transferring to the adjacent well in column 3, repeating for subsequent wells.

NF-κB-inducible reporter gene assay (*2.7.26, Procedure C*)

Carry out the assay as described with the following modifications.

Test solution Dilute the preparation to be examined with assay medium to obtain a concentration of about 1000 ng/mL. Use this solution to prepare 11 test sample dilutions in the range 1.0-200.0 ng/mL (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

Reference solution Reconstitute the contents of 1 vial of *etanercept BRP* with sterilised *water for injections R* to obtain a concentration of 10 000 IU/mL. Further dilute with assay medium to obtain a concentration of 400 IU/mL. Use this solution to prepare 10 additional reference sample dilutions (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

L929 cytotoxicity assay (*2.7.26, Procedure D*)

Carry out the assay as described with the following modifications.

Test solution Dilute the preparation to be examined with assay medium to obtain a concentration of 45 ng/mL. Use this solution to prepare 11 test sample dilutions, starting from 10 ng/mL (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

Reference solution Reconstitute the contents of 1 vial of *etanercept BRP* with sterilised *water for injections R* to obtain a concentration of 10 000 IU/mL. Further dilute with assay medium to obtain a concentration of 20 IU/mL. Use this solution to prepare 10 additional reference sample dilutions (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

STORAGE

In an airtight container at -20 °C or below.

LABELLING

The label states the content, in milligrams of protein per millilitre.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

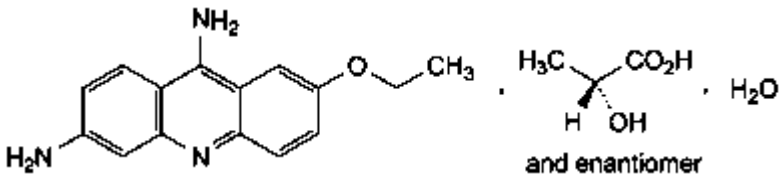
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethacridine Lactate Monohydrate

General Notices

(Ph. Eur. monograph 1591)



$C_{18}H_{21}N_3O_4,H_2O$ 361.4 *6402-23-9*

Action and use

Antiseptic.

Ph Eur

DEFINITION

7-Ethoxyacridine-3,9-diamine (2*RS*)-2-hydroxypropanoate monohydrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow crystalline powder.

Solubility

Sparingly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *ethacridine lactate monohydrate CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 5 mg of the substance to be examined in 2 mL of *water R* and dilute to 10 mL with *methanol R*.

Reference solution Dissolve 5 mg of *ethacridine lactate monohydrate CRS* in 2 mL of *water R* and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (17:17:66 *V/V/V*).

Application 2 µL; the volume can be adapted based on the type of plate used.

Development Over 2/3 of the plate.

Drying At 100-105 °C.

Detection A Examine in daylight.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

Detection B Examine in ultraviolet light at 254 nm and at 366 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 50 mL of solution S (see Tests) add 10 mL of *dilute sodium hydroxide solution R*. Filter. To 5 mL of the filtrate, add 1 mL of *dilute sulfuric acid R*. 5 mL of the solution obtained gives the reaction of lactates (*2.3.1*).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

pH (*2.2.3*)

5.5 to 7.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 1.0 g of *sodium octanesulfonate R* in a mixture of 300 mL of *acetonitrile R* and 700 mL of *phosphate buffer solution pH 2.8 R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 268 nm.

Injection 10 µL.

Run time 3 times the retention time of ethacridine.

Retention time Ethacridine = about 15 min.

Limits:

— *any impurity*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

4.5 per cent to 5.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.270 g in 5.0 mL of *anhydrous formic acid R*. Add 60.0 mL of *acetic anhydride R* and titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 34.34 mg of $C_{18}H_{21}N_3O_4$.

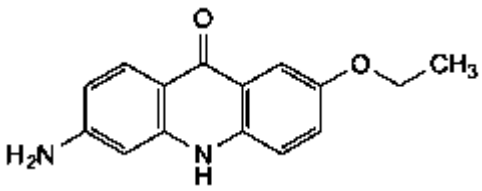
STORAGE

Protected from light.

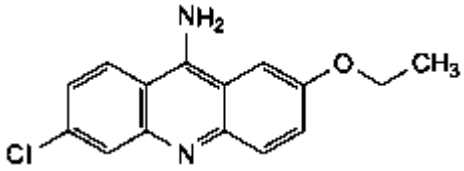
www.webofpharma.com

https://thuocngocanh.com/

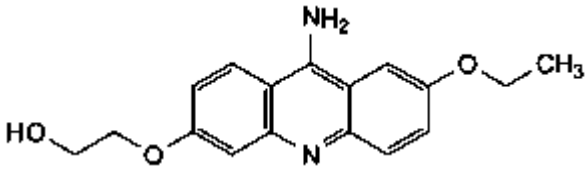
IMPURITIES



A. 6-amino-2-ethoxyacridin-9(10*H*)-one,



B. 6-chloro-2-ethoxyacridin-9-amine,



C. 2-[(9-amino-7-ethoxyacridin-3-yl)oxy]ethan-1-ol.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

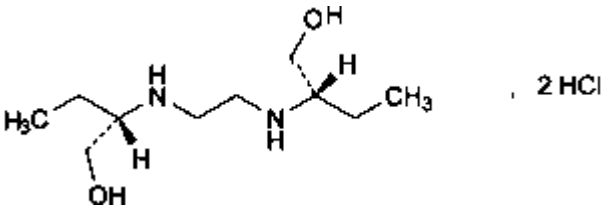
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethambutol Hydrochloride

General Notices

(Ph. Eur. monograph 0553)



$C_{10}H_{26}Cl_2N_2O_2$ 277.2 *1070-11-7*

Action and use

Antituberculosis drug.

Preparations

Ethambutol Oral Solution

Ethambutol Tablets

Ph Eur

DEFINITION

(2*S*,2′*S*)-2,2′-(Ethylenediimino)dibutan-1-ol dihydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: A, D, E.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ethambutol hydrochloride CRS*.

B. Examine the chromatograms obtained in the test for impurity A.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (b).

C. Dissolve 0.1 g in 10 mL of *water R*. Add 0.2 mL of *copper sulfate solution R* and 0.5 mL of *dilute sodium hydroxide solution R*; a blue colour is produced.

D. It gives reaction (a) of chlorides (2.3.1).

E. Related substances (see Tests).

TESTS

pH (2.2.3)

3.7 to 4.0.

Dissolve 0.2 g in 10 mL of *carbon dioxide-free water R*.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.50 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 50.0 mg of *aminobutanol R* (impurity A) in *methanol R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 50 mg of *ethambutol hydrochloride CRS* and 5 mg of *aminobutanol R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *water R*, *methanol R* (10:15:75 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air; heat at 110 °C for 10 min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Cool then spray with *ninhydrin solution R1*; heat at 110 °C for 5 min.

System suitability reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity A*: any spot due to impurity A in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (a) (1.0 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Suspend 4.0 mg of the substance to be examined in 4.0 mL of *acetonitrile R1* and add 100 µL of *triethylamine R*. Sonicate the mixture for 5 min. Add 15 µL of *(R)-(+)-α-methylbenzyl isocyanate R* and heat at 70 °C for 20 min.

Reference solution (a) Dilute 0.50 mL of the test solution to 100.0 mL with *acetonitrile R1*.

Reference solution (b) Treat 4.0 mg of *ethambutol for system suitability CRS* (containing impurity B) as described for the test solution.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, *water R* (50:50 *V/V*);

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	71	29
30 - 35	71 → 0	29 → 100
35 - 37	0	100
37 - 38	0 → 71	100 → 29

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 10 µL.

Relative retention With reference to ethambutol (retention time = about 14 min): impurity B = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to ethambutol and impurity B.

Limits:

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *unspecified impurities with a relative retention of 0.75 to 1.5 with reference to ethambutol*: for each impurity, not more than 0.2 times the area of the peak due to ethambutol in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total (impurity B and unspecified impurities with a relative retention of 0.75 to 1.5 with reference to ethambutol)*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the peak due to ethambutol in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurity D (1,2-dichloroethane) (2.4.24)

Maximum 5 ppm.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *water R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 27.72 mg of $C_{10}H_{26}Cl_2N_2O_2$.

STORAGE

In an airtight container.

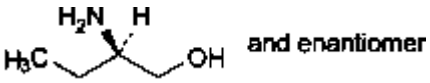
IMPURITIES

Specified impurities *A, B, D.*

www.webofpharma.com

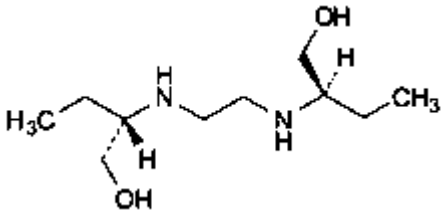
https://thuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.

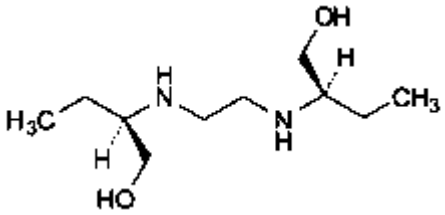


and enantiomer

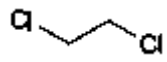
A. 2-aminobutan-1-ol,



B. (2*R*,2′*S*)-2,2′-(ethylenediimino)dibutan-1-ol (meso-ethambutol),



C. (2*R*,2′*R*)-2,2′-(ethylenediimino)dibutan-1-ol ((*R*,*R*)-ethambutol),



D. 1,2-dichloroethane (ethylene chloride).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethambutol Oral Solution

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Antituberculosis drug.

DEFINITION

Ethambutol Oral Solution is a solution of Ethambutol Hydrochloride in a suitable flavoured aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of ethambutol hydrochloride, $C_{10}H_{24}N_2O_2,2HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

B. To 10 mL of the oral solution add 2 mL of a 1% w/v solution of *copper(II) sulfate* followed by 1 mL of 1M *sodium hydroxide*; a blue colour is produced.

TESTS

2-Aminobutan-1-ol

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the oral solution containing 0.5 g of Ethambutol Hydrochloride to 10 mL with *methanol*.

(2) 0.05% w/v of *2-aminobutan-1-ol* in *methanol*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

www.webofpharma.com

https://nhathuocngocanh.com/

(e) After removal of the plate, allow it to dry in air, heat at 110° for 10 minutes and cool; spray with *ninhydrin solution R1* and heat at 110° for 5 minutes.

MOBILE PHASE

10 volumes of 13.5M *ammonia*, 15 volumes of *water* and 75 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to 2-aminobutan-1-ol is not more intense that the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral solution containing 80 mg of Ethambutol Hydrochloride with sufficient of a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water* to produce 100 mL.

(2) 0.08% w/v of *ethambutol hydrochloride BPCRS* in a mixture of 10 volumes of *acetonitrile* and 90 volumes of *water*

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed *with octadecylsilyl silica gel for chromatography* (5 µm) (ACE Excel Super C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 10 µL of each solution.

When the chromatograms are recorded under the prescribed conditions, the retention time of ethambutol is about 2.3 minutes.

MOBILE PHASE

10 volumes of *acetonitrile R1* and 90 volumes of a 0.21% w/v solution of *potassium dihydrogen orthophosphate* containing 0.1% w/v of *triethylamine*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{10}H_{24}N_2O_2$,2HCl, weight in volume, using the declared content of $C_{10}H_{24}N_2O_2$,2HCl in *ethambutol hydrochloride BPCRS*.

IMPURITIES

The impurity limited by the requirements of this monograph is: 2-aminobutan-1-ol.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethambutol Tablets

General Notices

Action and use

Antituberculosis drug.

DEFINITION

Ethambutol Tablets contain Ethambutol Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ethambutol hydrochloride, $C_{10}H_{24}N_2O_2,2HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 50 mg of ethambutol hydrochloride with 5 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ethambutol hydrochloride *(RS 134)*.

B. Shake a quantity of the powdered tablets containing 0.1 g of ethambutol hydrochloride with 10 mL of *water*, filter and add to the filtrate 2 mL of a 1% w/v solution of *copper(II) sulfate* followed by 1 mL of 1M *sodium hydroxide*. A blue colour is produced.

2-Aminobutanol

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 10 volumes of 13.5M *ammonia*, 15 volumes of *water* and 75 volumes of *methanol* as the mobile phase. Apply separately to the plate 2 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 0.50 g of ethambutol hydrochloride for 5 minutes with sufficient *methanol* to produce 10 mL. Solution (2) contains 0.050% w/v of *2-aminobutan-1-ol* in *methanol*. After removal of the plate, allow it to dry in air, heat at 110° for 10 minutes, cool, spray with *ninhydrin solution R1* and heat at 110° for 5 minutes. Any spot corresponding to 2-aminobutanol in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. Add 20 mL of 2M *sodium hydroxide* to a quantity of the powdered tablets containing 0.2 g of ethambutol hydrochloride, mix with the aid of ultrasound for 5 minutes and extract with three successive 25 mL quantities of a mixture of 3 volumes of *chloroform* and 1 volume of *propan-2-ol*. Filter each extract successively through the same filter consisting of *anhydrous sodium sulfate* on an absorbent cotton plug moistened with a mixture of 3 volumes of *chloroform* and 1 volume of *propan-2-ol* and wash the plug with 10 mL

www.webofpharma.com

https://thuocngocanh.com/

of the same solvent mixture. Add 100 mL of *anhydrous acetic acid* to the combined extracts and washings and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *1-naphtholbenzein solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 13.86 mg of $C_{10}H_{24}N_2O_2,2HCl$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethanol[1]

General Notices

Absolute Alcohol

Dehydrated Alcohol

(Anhydrous Ethanol, Ph. Eur. monograph 1318)

C_2H_6O 46.07 *64-17-5*

Ph Eur

DEFINITION

Content

Not less than 99.5 per cent *V/V* of C_2H_6O (99.2 per cent *m/m*), at 20 °C, calculated from the relative density using the alcoholimetric tables (*5.5*).

♦ CHARACTERS

Appearance

Colourless, clear, volatile, flammable liquid, hygroscopic.

Solubility

Miscible with water and with methylene chloride.

It burns with a blue, smokeless flame.

bp

About 78 °C.♦

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Relative density (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of anhydrous ethanol*.

◊ C. Mix 0.1 mL with 1 mL of a 10 g/L solution of *potassium permanganate R* and 0.2 mL of *dilute sulfuric acid R* in a test-tube. Cover immediately with a filter paper moistened with a freshly prepared solution containing 0.1 g of *sodium nitroprusside R* and 0.5 g of *piperazine hydrate R* in 5 mL of *water R*. After a few minutes, an intense blue colour appears on the paper and becomes paler after 10-15 min.

D. To 0.5 mL add 5 mL of *water R*, 2 mL of *dilute sodium hydroxide solution R*, then slowly add 2 mL of *0.05 M iodine*. A yellow precipitate is formed within 30 min.◊

TESTS

Appearance

It is clear (2.2.1) and colourless (2.2.2, Method II) when compared with *water R*. Dilute 1.0 mL to 20 mL with *water R*. After standing for 5 min, the dilution remains clear (2.2.1) when compared with *water R*.

Acidity or alkalinity

To 20 mL add 20 mL of *carbon dioxide-free water R* and 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Add 1.0 mL of *0.01 M sodium hydroxide*. The solution is pink (30 ppm, expressed as acetic acid).

Relative density (2.2.5)

0.790 to 0.793.

Absorbance (2.2.25)

Maximum 0.40 at 240 nm, 0.30 between 250 nm and 260 nm, and 0.10 between 270 nm and 340 nm. The spectrum shows a steadily descending curve with no observable peaks or shoulders.

Examine between 235 nm and 340 nm in a 5 cm cell using *water R* as the compensation liquid.

Volatile impurities

Gas chromatography (2.2.28).

Test solution (a) The substance to be examined.

Test solution (b) Add 150 µL of *4-methylpentan-2-ol R* to 500.0 mL of the substance to be examined.

Reference solution (a) Dilute 100 µL of *anhydrous methanol R* to 50.0 mL with the substance to be examined. Dilute 5.0 mL of the solution to 50.0 mL with the substance to be examined.

Reference solution (b) Dilute 50 µL of *anhydrous methanol R* and 50 µL of *acetaldehyde R* to 50.0 mL with the substance to be examined. Dilute 100 µL of the solution to 10.0 mL with the substance to be examined.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (c) Dilute 150 µL of *acetal R* to 50.0 mL with the substance to be examined. Dilute 100 µL of the solution to 10.0 mL with the substance to be examined.

Reference solution (d) Dilute 100 µL of *benzene R* to 100.0 mL with the substance to be examined. Dilute 100 µL of the solution to 50.0 mL with the substance to be examined.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 1.8 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 35 cm/s.

Split ratio 1:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 12	40
	12 - 32	40 → 240
	32 - 42	240
Injection port		200
Detector		280

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the 1st peak (acetaldehyde) and the 2nd peak (methanol).

Limits:

— *methanol* in the chromatogram obtained with test solution (a): not more than half the area of the corresponding peak in the chromatogram obtained with reference solution (a) (200 ppm *V/V*);

— *acetaldehyde + acetal*: maximum 10 ppm *V/V*, expressed as acetaldehyde.

www.webofpharma.com

https://thuocngocanh.com/

Calculate the sum of the contents of acetaldehyde and acetal in parts per million *V/V* using the following expression:

$$\frac{10 \times A_E}{A_T - A_E} + \frac{30 \times C_E}{C_T - C_E} \times \frac{44.05}{118.2}$$

A_E = area of the peak due to acetaldehyde in the chromatogram obtained with test solution (a),

A_T = area of the peak due to acetaldehyde in the chromatogram obtained with reference solution (b),

C_E = area of the peak due to acetal in the chromatogram obtained with test solution (a),

C_T = area of the peak due to acetal in the chromatogram obtained with reference solution (c),

44.05 = molecular mass of acetaldehyde,

118.2 = molecular mass of acetal.

— *benzene*: maximum 2 ppm *V/V*.

Calculate the content of benzene in parts per million *V/V* using the following expression:

$$\frac{2B_E}{B_T - B_E}$$

B_E = area of the peak due to benzene in the chromatogram obtained with test solution (a),

B_T = area of the peak due to benzene in the chromatogram obtained with reference solution (d).

If necessary, the identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

— *total of other impurities* in the chromatogram obtained with test solution (b): not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with test solution (b) (300 ppm);

— *disregard limit*: 0.03 times the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with test solution (b) (9 ppm).

Residue on evaporation

Maximum 25 ppm *m/V*.

Evaporate 100 mL to dryness on a water-bath and dry at 100-105 °C for 1 h. The residue weighs a maximum of 2.5 mg.

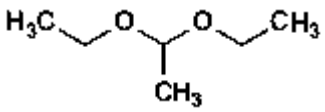
STORAGE

Protected from light.

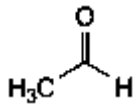
◊ IMPURITIES

www.webofpharma.com

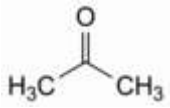
https://thuocngocanh.com/



A. 1,1-diethoxyethane (acetal),



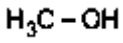
B. acetaldehyde,



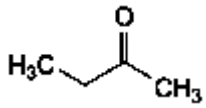
C. propan-2-one (acetone),

D. benzene,

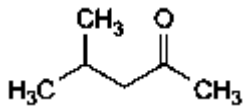
E. cyclohexane,



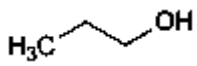
F. methanol,



G. butan-2-one (methyl ethyl ketone),



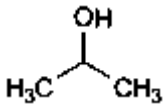
H. 4-methylpentan-2-one (methyl isobutyl ketone),



I. propan-1-ol (propanol),

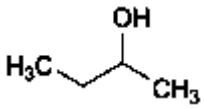
www.webofpharma.com

https://thuocngocanh.com/

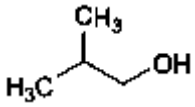


J. propan-2-ol (isopropyl alcohol),

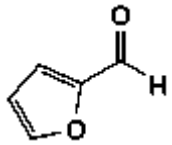
K. butan-1-ol (butanol),



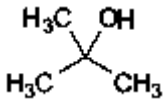
L. butan-2-ol,



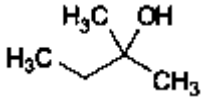
M. 2-methylpropan-1-ol (isobutanol),



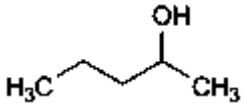
N. furane-2-carbaldehyde (furfural),



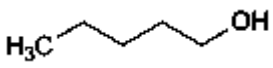
O. 2-methylpropan-2-ol (1,1-dimethylethyl alcohol),



P. 2-methylbutan-2-ol,



Q. pentan-2-ol,

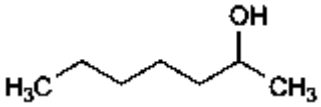


R. pentan-1-ol (pentanol),

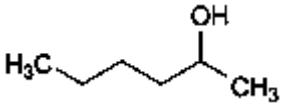
www.webofpharma.com

https://thuocngocanh.com/

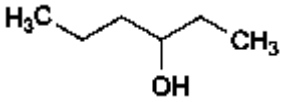
S. hexan-1-ol (hexanol),



T. heptan-2-ol,



U. hexan-2-ol,



V. hexan-3-ol.◊

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethanol (96 per cent)[1]

General Notices

Alcohol (96 per cent)

(Ph. Eur. monograph 1317)

Ph Eur

DEFINITION

Content

— *ethanol* (C_2H_6O; M_r 46.07): 95.1 per cent *V/V* (92.6 per cent *m/m*) to 96.9 per cent *V/V* (95.2 per cent *m/m*) at 20 °C, calculated from the relative density using the alcoholimetric tables (*5.5*);

— *water*.

♦ CHARACTERS

Appearance

Colourless, clear, volatile, flammable liquid, hygroscopic.

Solubility

Miscible with water and with methylene chloride.

It burns with a blue, smokeless flame.

bp

About 78 °C.♦

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Relative density (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *Ph. Eur. reference spectrum of ethanol (96 per cent)*.

www.webofpharma.com

https://thuocngocanh.com/

◊ C. Mix 0.1 mL with 1 mL of a 10 g/L solution of *potassium permanganate R* and 0.2 mL of *dilute sulfuric acid R* in a test-tube. Cover immediately with a filter paper moistened with a freshly prepared solution containing 0.1 g of *sodium nitroprusside R* and 0.5 g of *piperazine hydrate R* in 5 mL of *water R*. After a few minutes, an intense blue colour appears on the paper and becomes paler after 10-15 min.

D. To 0.5 mL add 5 mL of *water R*, 2 mL of *dilute sodium hydroxide solution R*, then slowly add 2 mL of *0.05 M iodine*. A yellow precipitate is formed within 30 min.◊

TESTS

Appearance

It is clear (*2.2.1*) and colourless (*2.2.2, Method II*) when compared with *water R*. Dilute 1.0 mL to 20 mL with *water R*. After standing for 5 min, the dilution remains clear (*2.2.1*) when compared with *water R*.

Acidity or alkalinity

To 20 mL add 20 mL of *carbon dioxide-free water R* and 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Add 1.0 mL of *0.01 M sodium hydroxide*. The solution is pink (30 ppm, expressed as acetic acid).

Relative density (*2.2.5*)

0.805 to 0.812.

Absorbance (*2.2.25*)

Maximum 0.40 at 240 nm, 0.30 between 250 nm and 260 nm, and 0.10 between 270 nm and 340 nm. The spectrum shows a steadily descending curve with no observable peaks or shoulders.

Examine between 235 nm and 340 nm, in a 5 cm cell using *water R* as the compensation liquid.

Volatile impurities

Gas chromatography (*2.2.28*).

Test solution (a) The substance to be examined.

Test solution (b) Add 150 µL of *4-methylpentan-2-ol R* to 500.0 mL of the substance to be examined.

Reference solution (a) Dilute 100 µL of *anhydrous methanol R* to 50.0 mL with the substance to be examined. Dilute 5.0 mL of the solution to 50.0 mL with the substance to be examined.

Reference solution (b) Dilute 50 µL of *anhydrous methanol R* and 50 µL of *acetaldehyde R* to 50.0 mL with the substance to be examined. Dilute 100 µL of the solution to 10.0 mL with the substance to be examined.

Reference solution (c) Dilute 150 µL of *acetal R* to 50.0 mL with the substance to be examined. Dilute 100 µL of the solution to 10.0 mL with the substance to be examined.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dilute 100 µL of *benzene R* to 100.0 mL with the substance to be examined. Dilute 100 µL of the solution to 50.0 mL with the substance to be examined.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R* (film thickness 1.8 µm).

Carrier gas *helium for chromatography R*.

Linear velocity 35 cm/s.

Split ratio 1:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 12	40
	12 - 32	40 → 240
	32 - 42	240
Injection port		200
Detector		280

Detection Flame ionisation.

Injection 1 µL.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the 1st peak (acetaldehyde) and the 2nd peak (methanol).

Limits:

— *methanol* in the chromatogram obtained with test solution (a): not more than half the area of the corresponding peak in the chromatogram obtained with reference solution (a) (200 ppm *V/V*);

— *acetaldehyde* + *acetal*: maximum 10 ppm *V/V*, expressed as acetaldehyde.

Calculate the sum of the contents of acetaldehyde and acetal in parts per million *V/V* using the following expression:

$$\frac{10 \times A_E}{A_{T\text{-}A_E}} + \frac{30 \times C_E}{C_{T\text{-}C_E}} \times \frac{44.05}{118.2}$$

www.webofpharma.com

https://thuvienthuocngocanh.com/

A_E = area of the peak due to acetaldehyde in the chromatogram obtained with test solution (a),

A_T = area of the peak due to acetaldehyde in the chromatogram obtained with reference solution (b),

C_E = area of the peak due to acetal in the chromatogram obtained with test solution (a),

C_T = area of the peak due to acetal in the chromatogram obtained with reference solution (c),

44.05 = molecular mass of acetaldehyde,

118.2 = molecular mass of acetal.

— *benzene*: maximum 2 ppm *V/V*.

Calculate the content of benzene in parts per million *V/V* using the following expression:

$$\frac{2B_E}{B_T - B_E}$$

B_E = area of the peak due to benzene in the chromatogram obtained with test solution (a),

B_T = area of the peak due to benzene in the chromatogram obtained with reference solution (d).

If necessary, the identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

— *total of other impurities* in the chromatogram obtained with test solution (b): not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with test solution (b) (300 ppm),

— *disregard limit*: 0.03 times the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with test solution (b) (9 ppm).

Residue on evaporation

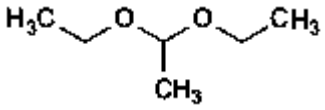
Maximum 25 ppm *m/V*.

Evaporate 100 mL to dryness on a water-bath and dry at 100-105 °C for 1 h. The residue weighs a maximum of 2.5 mg.

STORAGE

Protected from light.

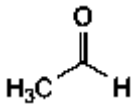
◊ IMPURITIES



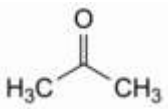
A. 1,1-diethoxyethane (acetal),

www.webofpharma.com

https://thuocngocanh.com/



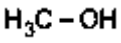
B. acetaldehyde,



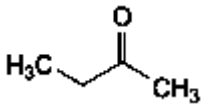
C. propan-2-one (acetone),

D. benzene,

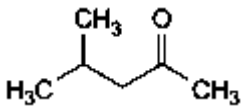
E. cyclohexane,



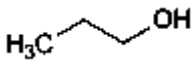
F. methanol,



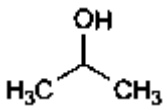
G. butan-2-one (methyl ethyl ketone),



H. 4-methylpentan-2-one (methyl isobutyl ketone),



I. propan-1-ol (propanol),

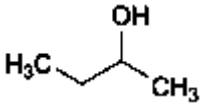


J. propan-2-ol (isopropyl alcohol),

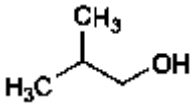
www.webofpharma.com

https://thuocngocanh.com/

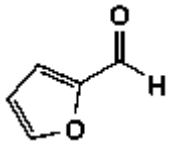
K. butan-1-ol (butanol),



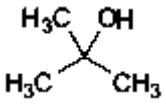
L. butan-2-ol,



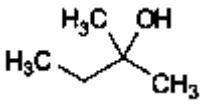
M. 2-methylpropan-1-ol (isobutanol),



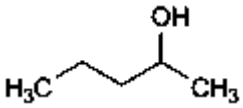
N. furane-2-carbaldehyde (furfural),



O. 2-methylpropan-2-ol (1,1-dimethylethyl alcohol),



P. 2-methylbutan-2-ol,



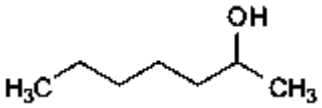
Q. pentan-2-ol,

R. pentan-1-ol (pentanol),

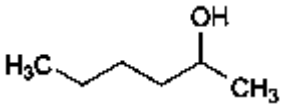
S. hexan-1-ol (hexanol),

www.webofpharma.com

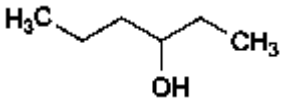
https://thuocngocanh.com/



T. heptan-2-ol,



U. hexan-2-ol,



V. hexan-3-ol.◊

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethanolamine

General Notices

Monoethanolamine

(Ph. Eur. monograph 2847)

C_2H_7NO 61.08 *141-43-5*

Action and use

Sclerosant.

Preparation

Ethanolamine Oleate Injection

Ph Eur

DEFINITION

2-Aminoethan-1-ol.

Content

99.0 per cent *m/m* to 101.0 per cent *m/m* (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless or pale yellow, viscous liquid, very hygroscopic.

Solubility

Miscible with water and with ethanol (96 per cent), slightly soluble in methylene chloride.

IDENTIFICATION

First identification *C*.

www.webofpharma.com

https://thuocngocanh.com/

Second identification *A, B.*

A. Relative density (2.2.5): 1.016 to 1.019.

B. Refractive index (2.2.6): 1.453 to 1.459.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *ethanolamine CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_6 (2.2.2, *Method II*).

Dissolve 12 g in *water R* and dilute to 20 mL with the same solvent.

Related substances

Gas chromatography (2.2.28).

Internal standard solution Dissolve 0.20 g of *3-aminopropanol R* in *methylene chloride R* and dilute to 200.0 mL with the same solvent.

Test solution Dissolve 1.0 g of the substance to be examined in the internal standard solution and dilute to 10.0 mL with the same solution. Transfer 1.0 mL of the solution to a ground-glass-stoppered test tube, then cool in an ice-bath. Slowly add 1.0 mL of *trifluoroacetic anhydride R*. Allow to stand at room temperature for 10 min.

Reference solution Dissolve 50 mg of the substance to be examined in the internal standard solution and dilute to 100.0 mL with the same solution. Transfer 1.0 mL of the solution to a ground-glass-stoppered test tube, then cool in an ice-bath. Slowly add 1.0 mL of *trifluoroacetic anhydride R*. Allow to stand at room temperature for 10 min.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.25 mm;

— *stationary phase*: *methylpolysiloxane R* (film thickness 0.25 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1 mL/min.

Split ratio 1:40.

Temperature:

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Column	0	80
	0 - 15	80 → 200
	15 - 25	200
Injection port		240
Detector		250

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to ethanolamine (retention time = about 4 min): 3-aminopropanol (internal standard) = about 1.4.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to ethanolamine and 3-aminopropanol.

Calculation of percentage contents Use the internal standard method.

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.25 per cent, determined on 2.00 g. Dissolve 10 g of *salicylic acid R* in 50 mL of the solvent.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 1.000 g in 70 mL of *carbon dioxide-free water R*. Titrate with *1 M hydrochloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *1 M hydrochloric acid* is equivalent to 61.08 mg of C_2H_7NO.

STORAGE

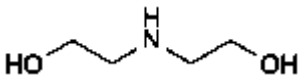
www.webofpharma.com

https://thuocngocanh.com/

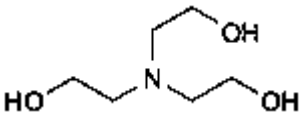
In an airtight container, protected from light.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



A. 2,2′-azanediyldi(ethan-1-ol),



B. 2,2′,2″-nitrilotri(ethan-1-ol).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethanolamine Oleate Injection

General Notices

DEFINITION

Ethanolamine Oleate Injection is a sterile solution containing 5% w/v of Ethanolamine Oleate, prepared by the interaction of Ethanolamine and Oleic Acid, in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of oleic acid, $C_{18}H_{34}O_2$

3.9 to 4.5% w/v.

Content of ethanolamine, C_2H_7NO

0.85 to 0.95% w/v.

TESTS

Alkalinity

pH, 8.0 to 9.0, Appendix V L.

ASSAY

For oleic acid

To 10 mL add 20 mL of *0.05M sulfuric acid VS* and extract with three 25 mL volumes of *chloroform*, washing each extract with the same 10 mL of *water*. Reserve the aqueous solution and washings for the Assay for ethanolamine. Evaporate the combined extracts to dryness, dissolve the residue in *ethanol (96%)* previously neutralised to *phenolphthalein solution R1* and titrate with *0.1M sodium hydroxide VS* using *phenolphthalein solution R1* as indicator. Each mL of *0.1M sodium hydroxide VS* is equivalent to 28.25 mg of $C_{18}H_{34}O_2$.

For ethanolamine

Titrate the excess of acid in the combined aqueous solution and washings reserved in the Assay for oleic acid with *0.1M sodium hydroxide VS* using *methyl orange solution* as indicator. Each mL of *0.05M sulfuric acid VS* is equivalent to 6.108 mg of C_2H_7NO.

STORAGE

Ethanolamine Oleate Injection should be protected from light.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Ether

General Notices

(Ph. Eur. monograph 0650)

$C_4H_{10}O$ 74.1 *60-29-7*

Ph Eur

DEFINITION

Ethoxyethane (diethyl ether).

It may contain a suitable non-volatile antioxidant at a suitable concentration.

CHARACTERS

Appearance

Clear, colourless, volatile, very mobile liquid.

Solubility

Soluble in water, miscible with ethanol (96 per cent), with methylene chloride and with fatty oils.

It is highly flammable.

IDENTIFICATION

A. Relative density (see Tests).

B. Distillation range (see Tests).

TESTS

Acidity

To 20 mL of *ethanol (96 per cent) R* add 0.25 mL of *bromothymol blue solution R1* and, dropwise, *0.02 M sodium hydroxide* until a blue colour persists for 30 s. Add 25 mL of the substance to be examined, shake and add, dropwise, *0.02 M sodium hydroxide* until the blue

www.webofpharma.com

https://thuocngocanh.com/

colour reappears and persists for 30 s. Not more than 0.4 mL of *0.02 M sodium hydroxide* is required.

Relative density (*2.2.5*)

0.714 to 0.716.

Distillation range (*2.2.11*)

After ensuring that the substance to be examined complies with the test for peroxides It distils completely between 34.0 °C and 35.0 °C. Carry out the test using a suitable heating device and taking care to avoid directly heating the flask above the level of the liquid.

Acetone and aldehydes

To 10.0 mL in a ground-glass-stoppered cylinder add 1 mL of *alkaline potassium tetraiodomercurate solution R* and shake for 10 s. Allow to stand for 5 min, protected from light. The lower layer only shows a slight opalescence.

If the substance to be examined does not comply with the test, carry out a control test: *after ensuring that the substance to be examined complies with the test for peroxides*, distil 40 mL until only 5 mL remains. Collect the distillate in a receiver cooled in a bath of iced water and repeat the test described above using 10.0 mL of the distillate. The test is valid only if the lower layer of the control test shows only a slight opalescence.

Peroxides

Place 8 mL of *potassium iodide and starch solution R* in a 12 mL ground-glass-stoppered cylinder about 15 mm in diameter. Fill completely with the substance to be examined, mix and allow to stand protected from light for 30 min. No colour develops.

Non-volatile matter

Maximum 20 mg/L.

After ensuring that the substance to be examined complies with the test for peroxides Evaporate 50 mL to dryness on a water-bath and dry the residue in an oven at 100-105 °C. The residue weighs a maximum of 1 mg.

Volatile impurities

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution The substance to be examined.

Reference solution Dissolve 100 µL of *2-methylpentane R* and 100 µL of *3-methylpentane R* in the substance to be examined and dilute to 10.0 mL with the substance to be examined. Dilute 300 µL of the solution to 10.0 mL with the substance to be examined.

Column:

— *material*: fused silica;

— *size*: *l* = 60 m, Ø = 0.32 mm;

— *stationary phase*: *phenylmethylpolysiloxane R* (film thickness 1.8 µm).

www.webofpharma.com

https://thuocngocanh.com/

Carrier gas *helium for chromatography R*.

Flow rate 1.5 mL/min.

Split ratio 1:40.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 10	35 → 40
	10 - 20	40 → 240
	20 - 35	240
Injection port		220
Detector		250

Detection Flame ionisation.

Injection 2.0 µL.

Relative retention With reference to ether (retention time = about 10.2 min): 2-methylpentane = about 1.18; 3-methylpentane = about 1.23.

System suitability Reference solution:

— *resolution*: minimum 3.0 between the peaks due to 2-methylpentane and 3-methylpentane.

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.1 per cent;

— *reporting threshold*: 0.03 per cent (peak due to 2-methylpentane in the chromatogram obtained with the reference solution).

Water (*2.5.12*)

Maximum 2 g/L, determined on 20 mL.

STORAGE

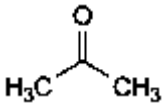
In an airtight container, protected from light.

IMPURITIES

www.webofpharma.com

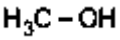
https://thuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D.*

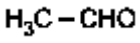


A. propan-2-one (acetone),

B. ethanol,



C. methanol,



D. acetaldehyde.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

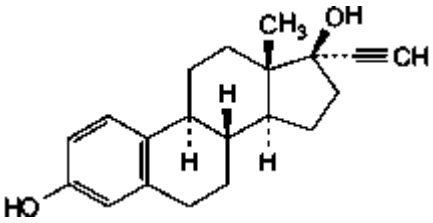
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethinylestradiol

General Notices

(Ph. Eur. monograph 0140)



$C_{20}H_{24}O_2$ 296.4 *57-63-6*

Action and use

Estrogen.

Preparations

Co-cyprindiol Tablets

Ethinylestradiol Tablets

Levonorgestrel and Ethinylestradiol Tablets

Ph Eur

DEFINITION

19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or slightly yellowish-white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent). It dissolves in dilute alkaline solutions.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ethinylestradiol CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Solvent mixture *methanol R*, *methylene chloride R* (10:90 *V/V*).

Test solution Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 25 mL with the solvent mixture.

Reference solution Dissolve 25 mg of *ethinylestradiol CRS* in the solvent mixture and dilute to 25 mL with the solvent mixture.

Plate *TLC silica gel G plate R*.

Mobile phase *ethanol (96 per cent) R*, *toluene R* (10:90 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air until the solvent has evaporated.

Detection Heat at 110 °C for 10 min, spray the hot plate with *alcoholic solution of sulfuric acid R* and heat again at 110 °C for 10 min. Examine in daylight and in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour, fluorescence and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *water R*, *acetonitrile R1* (40:60 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 30 mL of *acetonitrile R1* and dilute to 50.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 2 mg of *estrone CRS* (impurity C) in 10.0 mL of the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture. Use 1.0 mL of this solution to dissolve the contents of a vial of *ethinylestradiol for system suitability CRS* (containing impurities B, F, H, I and K).

Reference solution (c) Dissolve 50.0 mg of *ethinylestradiol CRS* in 30 mL of *acetonitrile R1* and dilute to 50.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R1*, *water R* (30:70 *V/V*);

— *mobile phase B*: *water R*, *acetonitrile R1* (25:75 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	100	0
35 - 65	100 → 0	0 → 100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 30 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *ethinylestradiol for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, F, H, I and K.

Relative retention With reference to ethinylestradiol (retention time = about 35 min): impurity F = about 0.2; impurity H = about 0.5; impurity I = about 0.8; impurity B = about 0.88; impurity C = about 0.92; impurity K = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 1.2 between the peaks due to impurities I and B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.7; impurity I = 0.4;

www.webofpharma.com

https://thuocngocanh.com/

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities H, I, K*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities C, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{20}H_{24}O_2$ from the declared content of *ethinylestradiol CRS*.

STORAGE

Protected from light.

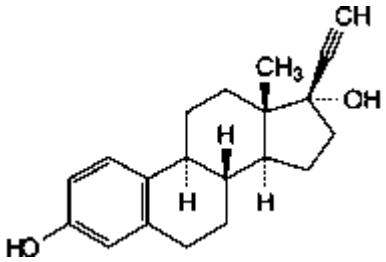
IMPURITIES

Specified impurities *B, C, F, H, I, K.*

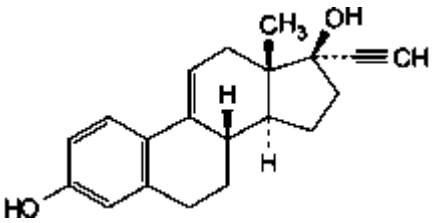
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E, G, J, L, M.*

www.webofpharma.com

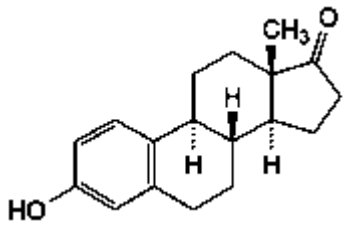
https://thuocngocanh.com/



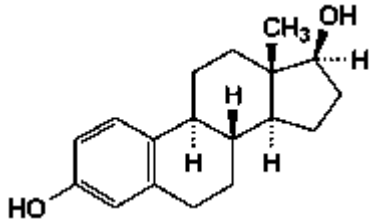
A. 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol (17β-ethinylestradiol),



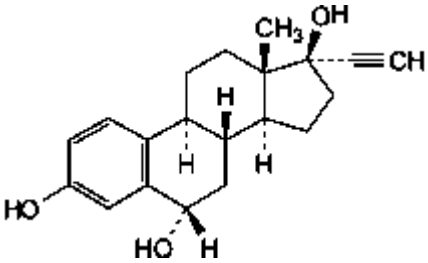
B. 19-nor-17α-pregna-1,3,5(10),9(11)-tetraen-20-yne-3,17-diol,



C. 3-hydroxyestra-1,3,5(10)-trien-17-one (estrone),



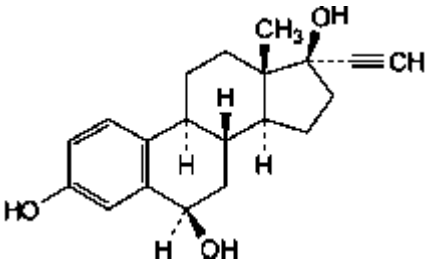
D. estra-1,3,5(10)-triene-3,17β-diol (estradiol),



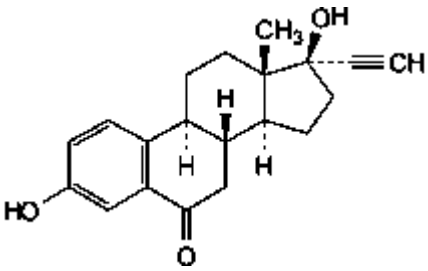
E. 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,6α,17-triol (6α-hydroxy-ethinylestradiol),

www.webofpharma.com

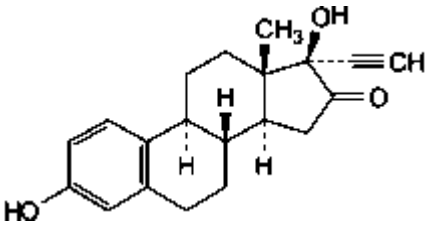
https://thuocngocanh.com/



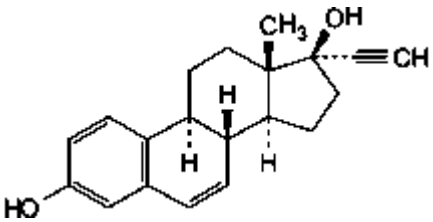
F. 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,6β,17-triol (6β-hydroxy-ethinylestradiol),



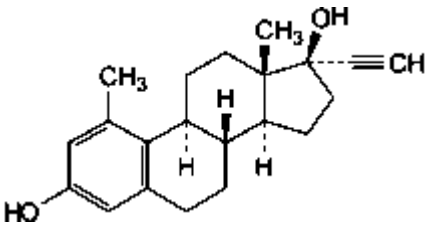
G. 3,17-dihydroxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-6-one (6-oxo-ethinylestradiol),



H. 3,17-dihydroxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-16-one (16-oxo-ethinylestradiol),



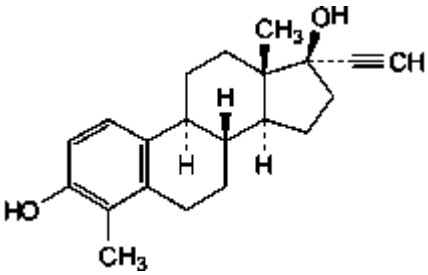
I. 19-nor-17α-pregna-1,3,5(10),6-tetraen-20-yne-3,17-diol,



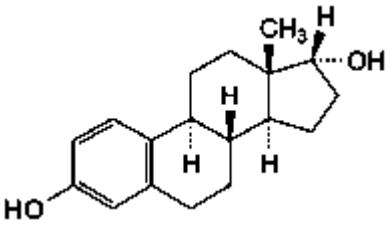
J. 1-methyl-19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol (1-methyl-ethinylestradiol),

www.webofpharma.com

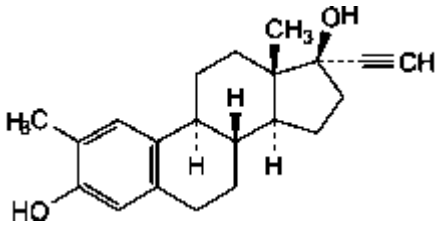
https://thuocngocanh.com/



K. 4-methyl-19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol (4-methyl-ethinylestradiol),



L. estra-1,3,5(10)-triene-3,17α-diol (17α-estradiol),



M. 2-methyl-19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol (2-methyl-ethinylestradiol).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethinylestradiol Tablets

General Notices

Action and use

Estrogen.

DEFINITION

Ethinylestradiol Tablets contain Ethinylestradiol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ethinylestradiol, $C_{20}H_{24}O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.25 mg of Ethinylestradiol with four 20-mL quantities of *acetone*, filter each extract in turn, evaporate the combined filtrates to dryness on a water bath in a current of *nitrogen* and dissolve the residue in 0.25 mL of *acetone*.

(2) 0.1% w/v of *ethinylestradiol BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with *ethanolic sulfuric acid (20%)*, heat at 110° for 10 minutes and examine under *ultraviolet light (365 nm)* and in daylight.

MOBILE PHASE

10 volumes of *ethanol (96%)* and 90 volumes of *toluene*.

CONFIRMATION

By each method of visualisation the principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. Triturate a quantity of the powdered tablets containing 0.1 mg of Ethinylestradiol with 0.5 mL of 0.1M *sodium hydroxide* and 5 mL of *water*, allow to stand for 5 minutes, filter, acidify the filtrate with 0.15 mL of *sulfuric acid*, add 3 mL of *ether*, shake and allow to separate. Evaporate the ether layer to dryness and heat the residue on a water bath for 5 minutes with 0.2 mL of *glacial acetic acid* and 2 mL of *orthophosphoric acid*. A pink colour with an intense orange fluorescence is produced.

TESTS

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Ethinylestradiol comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 2 mL of the mobile phase to one tablet, allow to stand for 5 minutes, mix with the aid of ultrasound for 5 minutes and centrifuge. Dilute the supernatant liquid with the mobile phase, if necessary, to produce a solution expected to contain 0.0005% w/v of Ethinylestradiol.
(2) 0.0005% w/v of *ethinylestradiol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 280 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of *water* and 60 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{24}O_2$ in each tablet using the declared content of $C_{20}H_{24}O_2$ in *ethinylestradiol BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

Ethinylestradiol tablets should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

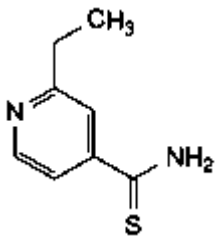
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ethionamide

General Notices

(Ph. Eur. monograph 0141)



$C_8H_{10}N_2S$ 166.2 *536-33-4*

Action and use

Antituberculosis drug.

Ph Eur

DEFINITION

2-Ethylpyridine-4-carbothioamide.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance Yellow, crystalline powder or small, yellow crystals.

Solubility Practically insoluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 158 °C to 164 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dissolve 10.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *methanol R*.

Spectral range 230-350 nm.

Absorption maximum At 290 nm.

Specific absorbance at the absorption maximum 380 to 440.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: ethionamide CRS.

D. Dissolve about 10 mg in 5 mL of *methanol R*. Add 5 mL of *silver nitrate solution R2*. A dark brown precipitate is formed.

TESTS

Acidity

Dissolve 2.0 g in 20 mL of *methanol R*, heating to about 50 °C, and add 20 mL of *water R*. Cool slightly while shaking until crystallisation begins and then allow to cool to room temperature. Add 60 mL of *water R* and 0.2 mL of *cresol red solution R*. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to red.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture Dissolve 0.240 g of *ammonium dihydrogen phosphate R* in 700 mL of *water R* and add 300 mL of *acetonitrile R*.

Test solution Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *pyridine-4-carbonitrile R* (impurity B) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *ethionamide for system suitability CRS* (containing impurity A) in reference solution (b) and dilute to 5.0 mL with reference solution (b).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 30 °C.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: dissolve 0.287 g of *ammonium dihydrogen phosphate R* in 850 mL of *water R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	85	15
30 - 32	85 → 70	15 → 30
32 - 55	70	30

Flow rate 1 mL/min.

Detection Spectrophotometer at 287 nm.

Injection 5 µL of the test solution and reference solutions (a) and (c).

Identification of impurities Use the chromatogram supplied with *ethionamide for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to ethionamide (retention time = about 9 min): impurity A = about 0.4; impurity B = about 0.5.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to impurities A and B.

Calculation of percentage contents:

— for each impurity, use the concentration of ethionamide in reference solution (a).

Limits:

— *impurity A*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

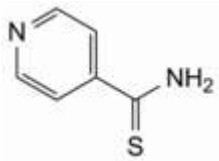
Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.62 mg of $C_8H_{10}N_2S$.

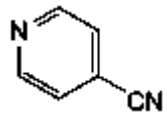
IMPURITIES

Specified impurities *A.*

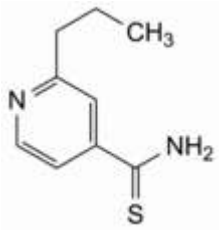
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, E, F.*



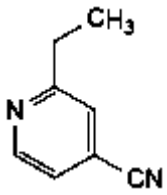
A. pyridine-4-carbothioamide,



B. pyridine-4-carbonitrile,



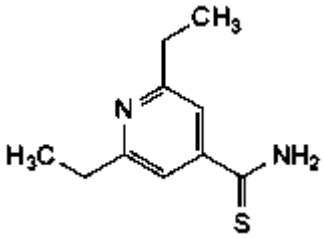
C. 2-propylpyridine-4-carbothioamide (prothionamide),



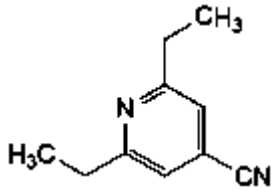
D. 2-ethylpyridine-4-carbonitrile,

www.webofpharma.com

https://thuocngocanh.com/



E. 2,6-diethylpyridine-4-carbothioamide,



F. 2,6-diethylpyridine-4-carbonitrile.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

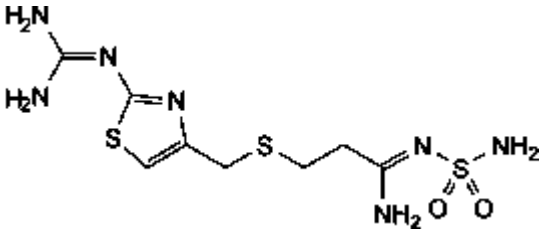
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Famotidine

General Notices

(Ph. Eur. monograph 1012)



$C_8H_{15}N_7O_2S_3$ 337.4 *76824-35-6*

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulceration.

Preparation

Famotidine Tablets

Ph Eur

DEFINITION

3-[[[2-[(Diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]-*N'*-sulfamoylpropanimidamide.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white, crystalline powder or crystals.

Solubility

Very slightly soluble in water, freely soluble in glacial acetic acid, very slightly soluble in anhydrous ethanol, practically insoluble in ethyl acetate. It dissolves in dilute mineral acids.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison famotidine CRS.

If the spectra obtained show differences, suspend 0.10 g of the substance to be examined and 0.10 g of the reference substance separately in 5 mL of water R. Heat to boiling and allow to cool, scratching the wall of the tube with a glass rod to initiate crystallisation. Filter, wash the crystals with 2 mL of iced water R and dry in an oven at 80 °C at a pressure not exceeding 670 Pa for 1 h. Record new spectra using the residues.

TESTS

Appearance of solution

Dissolve 0.20 g in a 50 g/L solution of hydrochloric acid R, heating to 40 °C if necessary, and dilute to 20 mL with the same acid. The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_7 (2.2.2, Method II).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 12.5 mg of the substance to be examined in mobile phase A and dilute to 25.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 2.5 mg of famotidine impurity D CRS in methanol R and dilute to 10.0 mL with the same solvent. To 1.0 mL of the solution add 0.50 mL of the test solution and dilute to 100.0 mL with mobile phase A.

Reference solution (c) Dissolve 5.0 mg of famotidine for system suitability CRS (containing impurities A, B, C, D, F and G) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 6 volumes of methanol R, 94 volumes of acetonitrile R and 900 volumes of a 1.882 g/L solution of sodium hexanesulfonate R previously adjusted to pH 3.5 with acetic acid R;

— *mobile phase B*: acetonitrile R;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Flow rate (mL/min)
0 - 23	100 → 96	0 → 4	1
23 - 27	96	4	1 → 2
27 - 47	96 → 78	4 → 22	2

Detection Spectrophotometer at 265 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *famotidine for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, F and G; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to famotidine (retention time = about 21 min): impurity D = about 1.1; impurity C = about 1.2; impurity G = about 1.4; impurity F = about 1.5; impurity A = about 1.6; impurity B = about 2.0.

System suitability:

— *retention time*: famotidine = 19-23 min in all the chromatograms;

— *resolution*: minimum 3.5 between the peaks due to famotidine and impurity D in the chromatogram obtained with reference solution (b).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.9; impurity B = 2.5; impurity C = 1.9; impurity F = 1.7; impurity G = 1.4;

— *impurities C, D*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities A, B, F, G*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 80 °C at a pressure not exceeding 670 Pa for 5 h.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.120 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.87 mg of $C_8H_{15}N_7O_2S_3$.

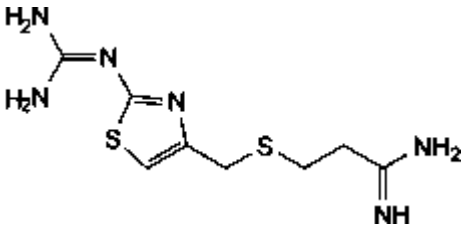
STORAGE

Protected from light.

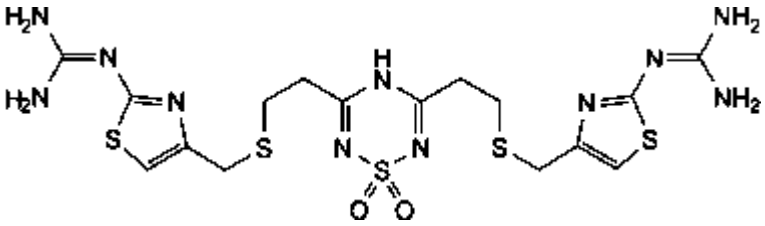
IMPURITIES

Specified impurities *A, B, C, D, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, H, I, J.*



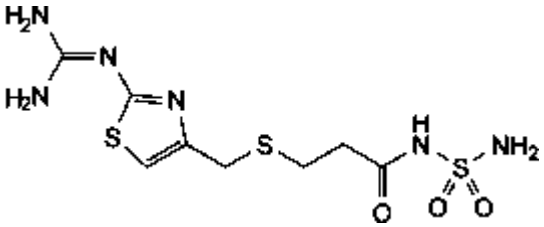
A. 3-[[[2-[(diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]propanimidamide,



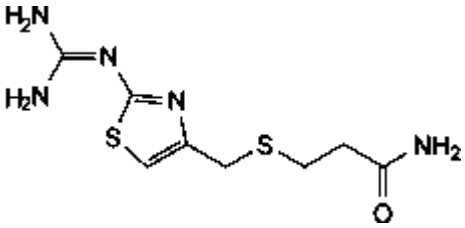
B. 3,5-bis[2-[[[2-[(diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]ethyl]-4*H*-1,2,4,6-thiatriazine 1,1-dioxide,

www.webofpharma.com

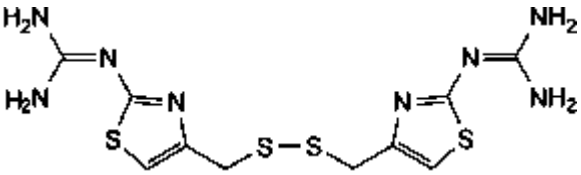
https://thuocngocanh.com/



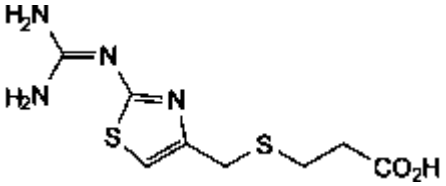
C. 3-[[[2-[(diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]-*N*-sulfamoylpropanamide,



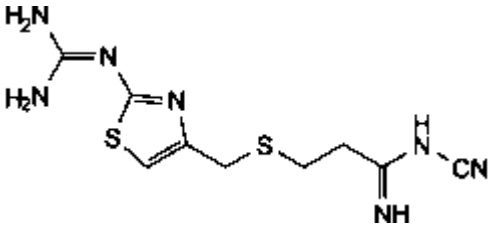
D. 3-[[[2-[(diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]propanamide,



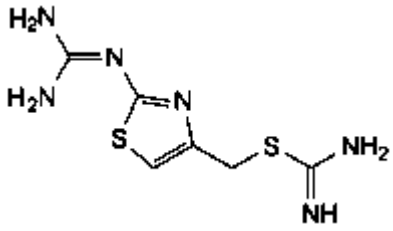
E. 2,2′-[disulfanediylbis(methylenethiazole-4,2-diyl)]diguanidine,



F. 3-[[[2-[(diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]propanoic acid,



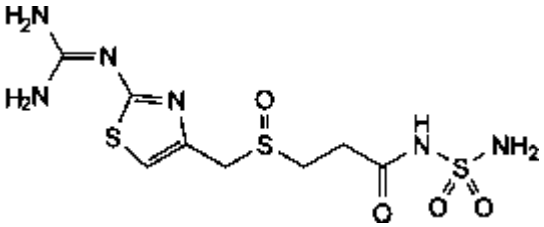
G. *N*-cyano-3-[[[2-[(diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]propanimidamide,



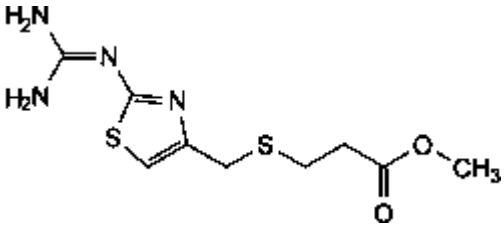
H. [2-[(diaminomethylidene)amino]thiazol-4-yl]methyl carbamimidothioate,

www.webofpharma.com

https://thuvienthuocngocanh.com/



I. 3-[[[2-[(diaminomethylidene)amino]thiazol-4-yl]methyl]sulfinyl]-*N*-sulfamoylpropanamide,



J. methyl 3-[[[2-[(diaminomethylidene)amino]thiazol-4-yl]methyl]sulfanyl]propanoate.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Famotidine Tablets

General Notices

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulceration.

DEFINITION

Famotidine Tablets contain Famotidine.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of famotidine, $C_8H_{15}N_7O_2S_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak in the chromatogram obtained with solution (2).

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 40 mg of Famotidine with 4 mL of *glacial acetic acid* with the aid of ultrasound, dilute to 10 mL with the same solvent, centrifuge and use the clear supernatant liquid.

(2) 0.4% w/v of *famotidine BPCRS* in *glacial acetic acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Fischer Silica Gel GF plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of 13.5M *ammonia*, 20 volumes of *toluene*, 25 volumes of *methanol* and 40 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

www.webofpharma.com

https://thuocngocanh.com/

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of phosphate buffer pH 4.5, at a temperature of 37°, as the medium prepared in the following manner. Dissolve 13.61 g of *potassium dihydrogen orthophosphate* in *water*, adjust the pH of the solution with *orthophosphoric acid* or 1M *potassium hydroxide* as necessary and add sufficient *water* to produce 1000 mL.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Withdraw a sample of the medium, filter and centrifuge at 2000 revolutions per minute for 20 minutes. Dilute, if necessary, with the dissolution medium to produce a solution expected to contain 0.001% w/v of Famotidine.

(2) 0.001% w/v of *famotidine BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS-2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.4 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 275 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

7 volumes of *acetonitrile* and a mixture of 93 volumes of 0.1M *sodium acetate* containing 0.1% v/v of *triethylamine* the pH adjusted to 6.0 with *glacial acetic acid*.

DETERMINATION OF CONTENT

Calculate the total content of famotidine, $C_8H_{15}N_7O_2S_3$, in the medium using the declared content of $C_8H_{15}N_7O_2S_3$ in *famotidine BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 0.05M *potassium dihydrogen orthophosphate* adjusted to pH 6.0 with 1M *potassium hydroxide*.

(1) Add 200 mL of solution A to a quantity of whole tablets containing 0.2 g of Famotidine, mix with the aid of ultrasound for 5 minutes, add about 200 mL of *methanol*, shake for 60 minutes and add sufficient solution A to produce 500 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) Dilute 1 volume of solution (1) to 10 volumes with solution A and dilute 1 volume of the resulting solution to 50 volumes with solution A.

www.webofpharma.com

https://thuocngocanh.com/

(4) Add 40 mL of *acetonitrile* to a mixture of 2 mg of each of *famotidine impurity C BPCRS*, *famotidine degradation impurity 1 BPCRS* (famotidine impurity F) and *famotidine impurity D EPCRS* (famotidine degradation impurity 2) mix with the aid of ultrasound for 2 minutes, cool, add 40 mL of *methanol* and sufficient solution A to produce 200 mL. Dilute 1 volume of the resulting solution to 5 volumes with solution A.

(5) Dissolve 8 mg of *famotidine BPCRS* in 15 mL of solution A with the aid of ultrasound, cool and add sufficient solution A to produce 20 mL (solution B); to 1 mL of this solution add 0.05 mL of *hydrogen peroxide solution (10 vol)* (generates famotidine degradation impurity 3).

(6) Dilute 1 volume of solution B with 100 volumes of solution A and further dilute a suitable volume with an equal volume of solution (4).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

When the chromatograms are recorded under the prescribed conditions, the relative retention(s) with reference to famotidine (retention time about 5 minutes) are: famotidine degradation impurity 3, about 0.4; famotidine impurity F, about 0.6; famotidine impurity C, about 0.7; and famotidine impurity D, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6):

the *resolution* between the peaks due to famotidine impurity C and famotidine is at least 1.4;

the *resolution* between the peaks due to famotidine and famotidine impurity D is at least 1.4.

If this resolution is not achieved adjust the content of *acetonitrile* or decrease the concentration of sodium acetate in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the areas of any peaks corresponding to impurities C, D, or F are not greater than the areas of the corresponding peaks in the chromatogram obtained with solution (4) (0.5% of each);

the area of any peak corresponding to famotidine degradation impurity 3 is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%).

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

Solution A: 0.05M *potassium dihydrogen orthophosphate* adjusted to pH 6.0 with 1M *potassium hydroxide*.

(1) Add 200 mL of solution A to a quantity of whole tablets containing 0.2 g of Famotidine, mix with the aid of ultrasound for 5 minutes, add about 200 mL of *methanol*, shake for 60 minutes and add sufficient solution A to produce 500 mL. Dilute 1 volume of this solution to 5 volumes with solution A.

(2) Dissolve 8 mg of *famotidine BPCRS* in 4 mL of *methanol*, mix with the aid of ultrasound for 5 minutes and add sufficient solution A to produce 20 mL. Dilute 1 volume of this solution to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

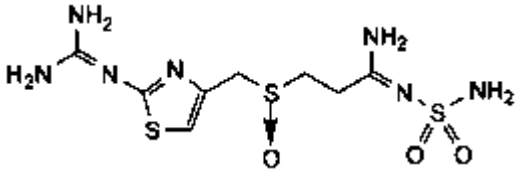
The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{15}N_7O_2S_3$ in the tablets using the declared content of $C_8H_{15}N_7O_2S_3$ in *famotidine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities C, D, and F listed under Famotidine and the following:



3. 3-[2-(Diaminomethyleneamino)-1,3-thiazol-4-ylmethylsulfinyl]-*N*-sulfamoylpropanamidine.

© Crown Copyright 2022

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Farmed Cod-liver Oil

General Notices

(Ph. Eur. monograph 2398)

Action and use

Source of vitamins A and D.

Ph Eur

DEFINITION

Purified fatty oil obtained from the fresh livers of farmed cod, *Gadus morhua* L., solid substances being removed by cooling and filtering.

Content

— *sum of the contents of EPA and DHA (expressed as triglycerides)*: 10.0 per cent to 28.0 per cent;

— *vitamin A*: 50 IU (15 µg) to 500 IU (150 µg) per gram;

— *vitamin D_3*: maximum 50 IU (1.3 µg) per gram.

A suitable antioxidant may be added.

PRODUCTION

The fish shall only be given feed with a composition that is in accordance with the relevant European Union or other applicable regulations.

The content of dioxins and dioxin-like PCBs (polychlorinated biphenyls) is controlled using methods and limits in accordance with the requirements set in the European Union or other applicable regulations.

CHARACTERS

Appearance

Clear, pale yellowish liquid.

Solubility

Practically insoluble in water, miscible with light petroleum, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Examine the ^{13}C NMR spectra obtained in the test for positional distribution (β(2)-acyl) of fatty acids (see Tests). The spectra contain peaks between 172 ppm and 173 ppm with shifts similar to those in the spectrum shown in Figure 2398.-1.
The positional distribution (β(2)-acyl) for cervonic (docosahexaenoic) acid (C22:6 n-3; DHA), timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA) and moroctic acid (C18:4 n-3) complies with the limits.

B. Linoleic acid (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 2.0.

Anisidine value (*2.5.36*)

Maximum 10.0.

Peroxide value (*2.5.5, Method B*)

Maximum 5.0.

Unsaponifiable matter (*2.5.7*)

Maximum 1.5 per cent, determined on 2.0 g, and extracting with 3 quantities, each of 50 mL, of *peroxide-free ether R*.

Stearin

Heat at least 10 mL to 60-90 °C then allow to cool for 3 h in a bath of iced water or a thermostatically controlled bath at 0 ± 0.5 °C. If necessary, to eliminate insoluble matter, filter the sample after heating. The sample remains clear.

Positional distribution (β(2)-acyl) of fatty acids

Nuclear magnetic resonance spectrometry (*2.2.33*).

Test solution Dissolve 190-210 mg of the substance to be examined in 500 µL of *deuterated chloroform R*. Prepare at least 3 samples and examine within 3 days.

Apparatus High-resolution FT-NMR spectrometer operating at minimum 300 MHz.

Acquisition of ^{13}C NMR spectra The following parameters may be used:

— *sweep width*: 200 ppm (-5 ppm to 195 ppm);

— *irradiation frequency offset*: 95 ppm;

— *time domain*: 64 K;

— *pulse delay*: 2 s;

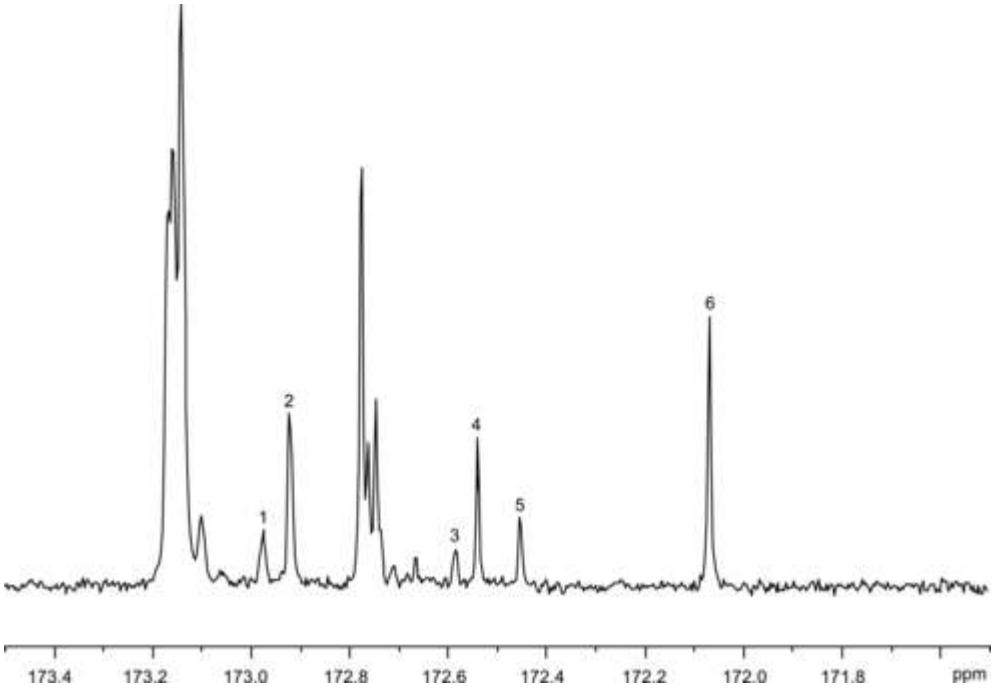
www.webofpharma.com

https://thuocngocanh.com/

— *pulse program*: zgig 30 (inverse gated, 30° excitation pulse);

— *dummy scans*: 4;

— *number of scans*: 4096.



1. α C18:4 2. α EPA 3. β C18:4 4. β EPA 5. α DHA 6. β DHA

Figure 2398.-1. – *^{13}C NMR spectrum: carbonyl region of farmed cod-liver oil*

Processing and plotting The following parameters may be used:

— *size*: 64 K (zero-filling);

— *window multiplication*: exponential;

— *Lorentzian broadening factor*: 0.2 Hz.

Use the $CDCl_3$ signal for shift referencing. The shift of the central peak of the 1:1:1 triplet is set to 77.16 ppm.

Plot the spectral region δ 171.5-173.5 ppm. Compare the spectrum with the spectrum shown in Figure 2398.-1. The shift values lie within the ranges given in Table 2398.-1.

Table 2398.-1. – *Shift values*

Signal	Shift range (ppm)
β DHA	172.05 - 172.09

www.webofpharma.com

https://thuocngocanh.com/

Signal	Shift range (ppm)
α DHA	172.43 - 172.47
β EPA	172.52 - 172.56
α EPA	172.90 - 172.94
β C18:4	172.56 - 172.60
α C18:4	172.95 - 172.99

System suitability:

— *signal-to-noise ratio*: minimum 5 for the smallest relevant peak corresponding to α C18:4 signal (in the range δ 172.95-172.99 ppm);

— *peak width at half-height*: maximum 0.02 ppm for the central $CDCl_3$ signal (at δ 77.16 ppm).

Calculation of positional distribution (β(2)-acyl) Use the following expression:

$$\frac{100 \times \beta}{\alpha + \beta}$$

α = peak area of the corresponding α-carbonyl peak;

β = peak area of β-carbonyl peak from C22:6 n-3, C20:5 n-3 or C18:4 n-3, respectively.

Limits:

— *positional distribution (β(2)-acyl)*:

— *cervonic (docosahexaenoic) acid (C22:6 n-3; DHA)*: 71 per cent to 81 per cent;

— *timnodonic (eicosapentaenoic) acid (C20:5 n-3 EPA)*: 32 per cent to 40 per cent;

— *moroctic acid (C18:4 n-3)*: 28 per cent to 38 per cent.

Composition of fatty acids (2.4.29)

For identification of the peaks, see the chromatogram shown in Figure 2398.-2.

The 24 largest peaks of the methyl esters account for more than 90 per cent of the total area (these correspond to, in common elution order: 14:0, 15:0, 16:0, 16:1 n-7, 16:4 n-1, 18:0, 18:1 n-9, 18:1 n-7, 18:2 n-6, 18:3 n-3, 18:4 n-3, 20:1 n-11, 20:1 n-9, 20:1 n-7, 20:2 n-6, 20:4 n-6, 20:3 n-3, 20:4 n-3, 20:5 n-3, 22:1 n-11, 22:1 n-9, 21:5 n-3, 22:5 n-3, 22:6 n-3).

Linoleic acid (2.4.29)

3.0 per cent to 11.0 per cent.

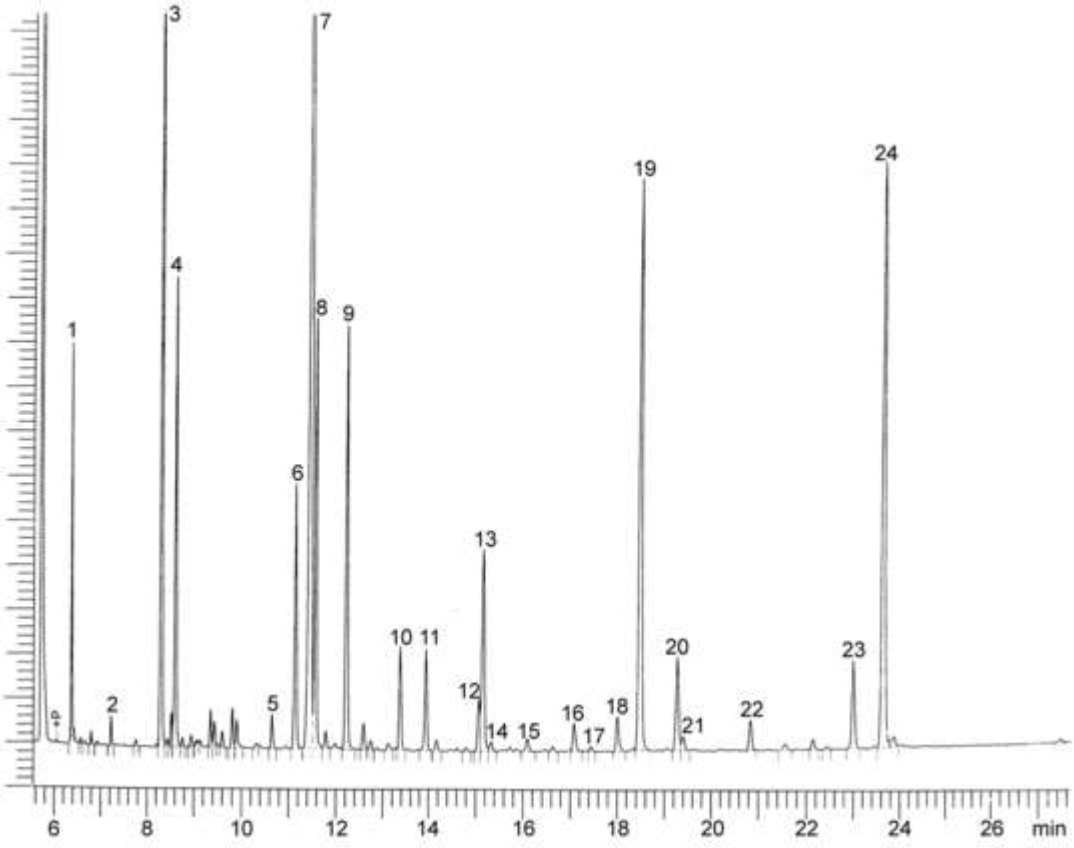
ASSAY

www.webofpharma.com

https://thuocngocanh.com/

EPA and DHA (2.4.29)

See the chromatogram shown in Figure 2398.-2.



1. C14:0	5. C16:4 n-1	9. C18:2 n-6	13. C20:1 n-9	17. C20:3 n-3	21. C22:1 n-9
2. C15:0	6. C18:0	10 C18:3 n-3	14. C20:1 n-7	18. C20:4 n-3	22. C21:5 n-3
3. C16:0	7. C18:1 n-9	11. C18:4 n-3	15. C20:2 n-6	19. C20:5 n-3	23. C22:5 n-3
4. C16:1 n-7	8. C18:1 n-7	12. C20:1 n-11	16. C20:4 n-6	20. C22:1 n-11	24. C22:6 n-3

Figure 2398.-2. – *Chromatogram for the test for composition of fatty acids of farmed cod-liver oil*

Vitamin A

Carry out the test as rapidly as possible, avoiding exposure to actinic light and air, oxidising agents, oxidation catalysts (for example, copper and iron) and acids.

Use method A. If method A is found not to be valid, use method B.

METHOD A

Ultraviolet absorption spectrophotometry (2.2.25).

www.webofpharma.com

https://thuocngocanh.com/

Test solution To 1.00 g in a round-bottomed flask, add 3 mL of a freshly prepared 50 per cent *m/m* solution of *potassium hydroxide R* and 30 mL of *anhydrous ethanol R*. Boil under reflux in a current of *nitrogen R* for 30 min. Cool rapidly and add 30 mL of *water R*. Extract with 50 mL of *ether R*. Repeat the extraction 3 times and discard the lower layer after complete separation. Wash the combined upper layers with 4 quantities, each of 50 mL, of *water R*, and evaporate to dryness under a gentle current of *nitrogen R* at a temperature not exceeding 30 °C or in a rotary evaporator at a temperature not exceeding 30 °C under reduced pressure (water ejector). Dissolve the residue in sufficient *2-propanol R1* to give an expected concentration of vitamin A equivalent to 10-15 IU/mL.

Measure the absorbances of the solution at 300 nm, 310 nm, 325 nm and 334 nm and at the wavelength of maximum absorption with a suitable spectrophotometer in specially matched 1 cm cells, using *2-propanol R1* as the compensation liquid.

Calculate the content of vitamin A, as all-*trans*-retinol, in International Units per gram, using the following expression:

$$A_{325} \times \frac{1821}{100m} \times V$$

A_{325}	=	absorbance at 325 nm;
m	=	mass of the substance to be examined, in grams;
V	=	total volume of solution containing 10-15 IU of vitamin A per millilitre;
1821	=	conversion factor for the specific absorbance of all-*trans*-retinol, in International Units.

The above expression can be used only if A_{325} has a value not greater than $A_{325,corr}$ /0.970, where $A_{325,corr}$ is the corrected absorbance at 325 nm and is given by the following equation:

$$A_{325,\,corr} = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$$

A designates the absorbance at the wavelength indicated by the subscript.

If A_{325} has a value greater than $A_{325,corr}$ /0.970, calculate the content of vitamin A using the following expression:

$$A_{325,\,corr} \times \frac{1821}{100m} \times V$$

The assay is not valid unless:

— the wavelength of maximum absorption lies between 323 nm and 327 nm;

— the absorbance at 300 nm relative to that at 325 nm is at most 0.73.

METHOD B

Liquid chromatography (*2.2.29*).

Test solution Prepare duplicates. To 2.00 g in a round-bottomed flask, add 5 mL of a freshly prepared 100 g/L solution of *ascorbic acid R*, 10 mL of a freshly prepared 800 g/L solution of *potassium hydroxide R* and 100 mL of *anhydrous ethanol R*. Boil under a reflux condenser on a water-bath for 15 min. Add 100 mL of a 10 g/L solution of *sodium chloride R* and cool. Transfer the solution to a 500 mL separating funnel, rinsing the round-bottomed flask with about 75 mL of a 10 g/L solution of *sodium chloride R* and then with 150 mL of a mixture of

www.webofpharma.com

https://thietbiuocngocanh.com/

equal volumes of *ether R* and *light petroleum R1*. Shake for 1 min. When the layers have separated completely, discard the lower layer and wash the upper layer, first with 50 mL of a 30 g/L solution of *potassium hydroxide R* in a 10 per cent *V/V* solution of *anhydrous ethanol R* and then with 3 quantities, each of 50 mL, of a 10 g/L solution of *sodium chloride R*. Filter the upper layer through 5 g of *anhydrous sodium sulfate R* on a fast filter paper into a 250 mL flask suitable for a rotary evaporator. Wash the funnel with 10 mL of fresh extraction mixture, filter and combine the upper layers. Distil them at a temperature not exceeding 30 °C under reduced pressure (water ejector) and fill with *nitrogen R* when evaporation is completed. Alternatively, evaporate the solvent under a gentle current of *nitrogen R* at a temperature not exceeding 30 °C. Dissolve the residue in *2-propanol R*, transfer to a 25 mL volumetric flask and dilute to 25 mL with *2-propanol R*. Gentle heating in an ultrasonic bath may be required. *A large fraction of the white residue is cholesterol, constituting approximately 50 per cent m/m of the unsaponifiable matter of cod-liver oil.*

Reference solution (a) Prepare a solution of *retinol acetate CRS* in *2-propanol R1* so that 1 mL contains about 1000 IU of all-*trans*-retinol.

The exact concentration of reference solution (a) is assessed by ultraviolet absorption spectrophotometry (*2.2.25*). Dilute reference solution (a) with *2-propanol R1* to a presumed concentration of 10-15 IU/mL and measure the absorbance at 326 nm in matched 1 cm cells using *2-propanol R1* as the compensation liquid.

Calculate the content of vitamin A in International Units per millilitre of reference solution (a) using the following expression, taking into account the assigned content of *retinol acetate CRS*:

$$A_{326} \times \frac{1900 \times V_2}{100 \times V_1}$$

A_{326} = absorbance at 326 nm;

V_1 = volume of reference solution (a) used;

V_2 = volume of the diluted solution;

1900 = conversion factor for the specific absorbance of *retinol acetate CRS*, in International Units.

Reference solution (b) Proceed as described for the test solution but using 2.00 mL of reference solution (a) in place of the substance to be examined.

The exact concentration of reference solution (b) is assessed by ultraviolet absorption spectrophotometry (*2.2.25*). Dilute reference solution (b) with *2-propanol R1* to a presumed all-*trans*-retinol concentration of 10-15 IU/mL and measure the absorbance at 325 nm in matched 1 cm cells using *2-propanol R1* as the compensation liquid.

Calculate the content of all-*trans*-retinol in International Units per millilitre of reference solution (b), using the following expression:

$$A_{325} \times \frac{1821 \times V_3}{100 \times V_4}$$

A_{325} = absorbance at 325 nm;

V_3 = volume of the diluted solution;

V_4 = volume of reference solution (b) used;

www.webofpharma.com

https://thuocngocanh.com/

1821 = conversion factor for the specific absorbance of all-*trans*-retinol, in International Units.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5-10 µm).

Mobile phase *water R*, *methanol R* (3:97 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 325 nm.

Injection 10 µL; inject in triplicate the test solution and reference solution (b).

Retention time All-*trans*-retinol = 5 ± 1 min.

System suitability:

— the chromatogram obtained with the test solution shows a peak corresponding to the peak due to all-*trans*-retinol in the chromatogram obtained with reference solution (b);

— the results obtained with the duplicate test solutions do not differ by more than 5 per cent;

— the recovery of all-*trans*-retinol in reference solution (b) as assessed by direct absorption spectrophotometry is greater than 95 per cent.

Calculate the content of vitamin A using the following expression:

$$A_1 \times \frac{C \times V}{A_2} \times \frac{1}{m}$$

A_1 = area of the peak due to all-*trans*-retinol in the chromatogram obtained with the test solution;

A_2 = area of the peak due to all-*trans*-retinol in the chromatogram obtained with reference solution (b);

C = concentration of *retinol acetate CRS* in reference solution (a) as assessed prior to the saponification, in International Units per millilitre (= 1000 IU/mL);

V = volume of reference solution (a) treated (2.00 mL);

m = mass of the substance to be examined in the test solution (2.00 g).

Vitamin D_3

Liquid chromatography (2.2.29). *Carry out the assay as rapidly as possible, avoiding exposure to actinic light and air.*

Internal standard solution Dissolve 0.50 mg of *ergocalciferol CRS* in 100 mL of *anhydrous ethanol R*.

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) To 4.00 g in a round-bottomed flask, add 5 mL of a freshly prepared 100 g/L solution of *ascorbic acid R*, 10 mL of a freshly prepared 800 g/L solution of *potassium hydroxide R* and 100 mL of *anhydrous ethanol R*. Boil under a reflux condenser on a water-bath for 30 min. Add 100 mL of a 10 g/L solution of *sodium chloride R* and cool the solution to room temperature. Transfer the solution to a 500 mL separating funnel, rinsing the round-bottomed flask with about 75 mL of a 10 g/L solution of *sodium chloride R* and then with 150 mL of a mixture of equal volumes of *ether R* and *light petroleum R1*. Shake for 1 min. When the layers have separated completely, discard the lower layer and wash the upper layer, first with 50 mL of a 30 g/L solution of *potassium hydroxide R* in a 10 per cent *V/V* solution of *anhydrous ethanol R*, and then with 3 quantities, each of 50 mL, of a 10 g/L solution of *sodium chloride R*. Filter the upper layer through 5 g of *anhydrous sodium sulfate R* on a fast filter paper into a 250 mL flask suitable for a rotary evaporator. Wash the funnel with 10 mL of fresh extraction mixture, filter and combine the upper layers. Distil them at a temperature not exceeding 30 °C under reduced pressure (water ejector) and fill with *nitrogen R* when evaporation is completed. Alternatively, evaporate the solvent under a gentle current of *nitrogen R* at a temperature not exceeding 30 °C. Dissolve the residue in 1.5 mL of the mobile phase described under Purification. Gentle heating in an ultrasonic bath may be required. *A large fraction of the white residue is cholesterol, constituting approximately 50 per cent m/m of the unsaponifiable matter of cod-liver oil.*

Test solution (b) Prepare duplicates. To 4.00 g add 2.0 mL of the internal standard solution and proceed as described for test solution (a).

Reference solution (a) Dissolve 0.50 mg of *cholecalciferol CRS* in 100.0 mL of *anhydrous ethanol R*.

Reference solution (b) In a round-bottomed flask, add 2.0 mL of reference solution (a) and 2.0 mL of the internal standard solution and proceed as described for test solution (a).

PURIFICATION

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *nitrile silica gel for chromatography R* (10 µm).

Mobile phase *isoamyl alcohol R*, *hexane R* (1.6:98.4 *V/V*).

Flow rate 1.1 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 350 µL of reference solution (b) and test solutions (a) and (b). Collect each eluate from 2 min before until 2 min after the retention time of cholecalciferol, in a ground-glass-stoppered tube containing 1 mL of a 1 g/L solution of *butylhydroxytoluene R* in *hexane R*. Evaporate separately to dryness at a temperature not exceeding 30 °C under a gentle current of *nitrogen R*. Dissolve each residue in 1.5 mL of *acetonitrile R*.

DETERMINATION

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

www.webofpharma.com

https://thietbiuocngocanh.com/

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *phosphoric acid R*, 96 per cent *V/V* solution of *acetonitrile R* (0.2:99.8 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 2 quantities not exceeding 200 µL of each of the 3 solutions obtained under Purification.

System suitability:

— *resolution*: minimum 1.4 between the peaks due to ergocalciferol and cholecalciferol in the chromatogram obtained with reference solution (b);

— the results obtained with the test solution (b) duplicates do not differ by more than 5 per cent.

Calculate the content of vitamin D_3 in International Units per gram using the following expression, taking into account the assigned content of *cholecalciferol CRS*:

$$\frac{A_2}{A_6} \times \frac{A_3}{A_4 - \left[\frac{A_5}{A_1}\right] \times A_2} \times \frac{m_2}{m_1} \times \frac{V_2}{V_1} \times 40$$

m_1 = mass of the sample in test solution (b), in grams;

m_2 = total mass of *cholecalciferol CRS* used for the preparation of reference solution (a), in micrograms (500 µg);

A_1 = area (or height) of the peak due to cholecalciferol in the chromatogram obtained with test solution (a);

A_2 = area (or height) of the peak due to cholecalciferol in the chromatogram obtained with test solution (b);

A_3 = area (or height) of the peak due to ergocalciferol in the chromatogram obtained with reference solution (b);

A_4 = area (or height) of the peak due to ergocalciferol in the chromatogram obtained with test solution (b);

A_5 = area (or height) of a possible peak in the chromatogram obtained with test solution (a) with the same retention time as the peak co-eluting with ergocalciferol in test solution (b);

A_6 = area (or height) of the peak due to cholecalciferol in the chromatogram obtained with reference solution (b);

V_1 = total volume of reference solution (a) (100 mL);

V_2 = volume of reference solution (a) used for preparing reference solution (b) (2.0 mL).

STORAGE

In an airtight and well-filled container, protected from light. If no antioxidant is added, store under an inert gas.

www.webofpharma.com

https://thuocngocanh.com/

Once the container has been opened, its contents are used as soon as possible and any part of the contents not used at once is protected by an atmosphere of inert gas.

LABELLING

The label states:

— the concentration of EPA and DHA, expressed as triglycerides;

— the number of International Units of vitamin A per gram;

— the number of International Units of vitamin D_3 per gram.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Farmed Salmon Oil

General Notices

(Ph. Eur. monograph 1910)

Ph Eur

DEFINITION

Purified fatty oil obtained from fresh farmed *Salmo salar*. The positional distribution (β(2)-acyl) is 60-70 per cent for cervonic (docosahexaenoic) acid (C22:6 n-3; DHA), 25-35 per cent for timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA) and 40-55 per cent for moroctic acid (C18:4 n-3).

Content

— *sum of the contents of EPA and DHA (expressed as triglycerides)*: 10.0 per cent to 28.0 per cent.

A suitable antioxidant may be added.

PRODUCTION

The fish shall only be given feed with a composition that is in accordance with the relevant European Union or other applicable regulations.

The content of dioxins and dioxin-like PCBs (polychlorinated biphenyls) is controlled using methods and limits in accordance with the requirements set in the European Union or other applicable regulations.

The oil is produced by mechanical expression of fresh raw materials, either from the whole fish, or fish where the fillets have been removed, at a temperature not exceeding 100 °C, and without using solvents. After centrifugation, solid substances may be removed from the oil by cooling and filtering (winterisation).

CHARACTERS

Appearance

Pale pink liquid.

Solubility

Practically insoluble in water, very soluble in acetone and in heptane, slightly soluble in anhydrous ethanol.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Examine the ^{13}C NMR spectra obtained in the assay for positional distribution (β(2)-acyl) of fatty acids. The spectra contain peaks between 172 ppm and 173 ppm with shifts similar to those in the type spectrum (Figure 1910.-2). The oil to be examined complies with the limits of this assay.

TESTS

Absorbance (2.2.25)

Minimum 0.10, measured at the absorption maximum between 470 nm and 480 nm.

Dissolve 5.0 mL in 5.0 mL of *trimethylpentane R*.

Acid value (2.5.1)

Maximum 2.0.

Anisidine value (2.5.36)

Maximum 10.0.

Peroxide value (2.5.5, Method A)

Maximum 5.0.

Unsaponifiable matter (2.5.7)

Maximum 1.5 per cent, determined on 5.0 g.

Linoleic acid (2.4.29)

Maximum 11.0 per cent.

Identify the peak due to linoleic acid using the chromatogram in Figure 1910.-1. Determine the percentage content by normalisation.

ASSAY

Positional distribution (β(2)-acyl) of fatty acids

Nuclear magnetic resonance spectrometry (2.2.33).

Apparatus High resolution FT-NMR spectrometer operating at minimum 300 MHz.

Test solution Dissolve 190-210 mg of fresh salmon oil in 500 µL of *deuterated chloroform R*. Prepare at least 3 samples and examine within 3 days.

Acquisition of ^{13}C NMR spectra The following parameters may be used:

— *sweep width*: 200 ppm (-5 to 195 ppm);

www.webofpharma.com

https://thuocngocanh.com/

— *irradiation frequency offset*: 95 ppm;

— *time domain*: 64 K;

— *pulse delay*: 2 s;

— *pulse program*: zgig 30 (inverse gated, 30° excitation pulse);

— *dummy scans*: 4;

— *number of scans*: 4096.

Processing and plotting The following parameters may be used:

— *size*: 64 K (zero-filling);

— *window multiplication*: exponential;

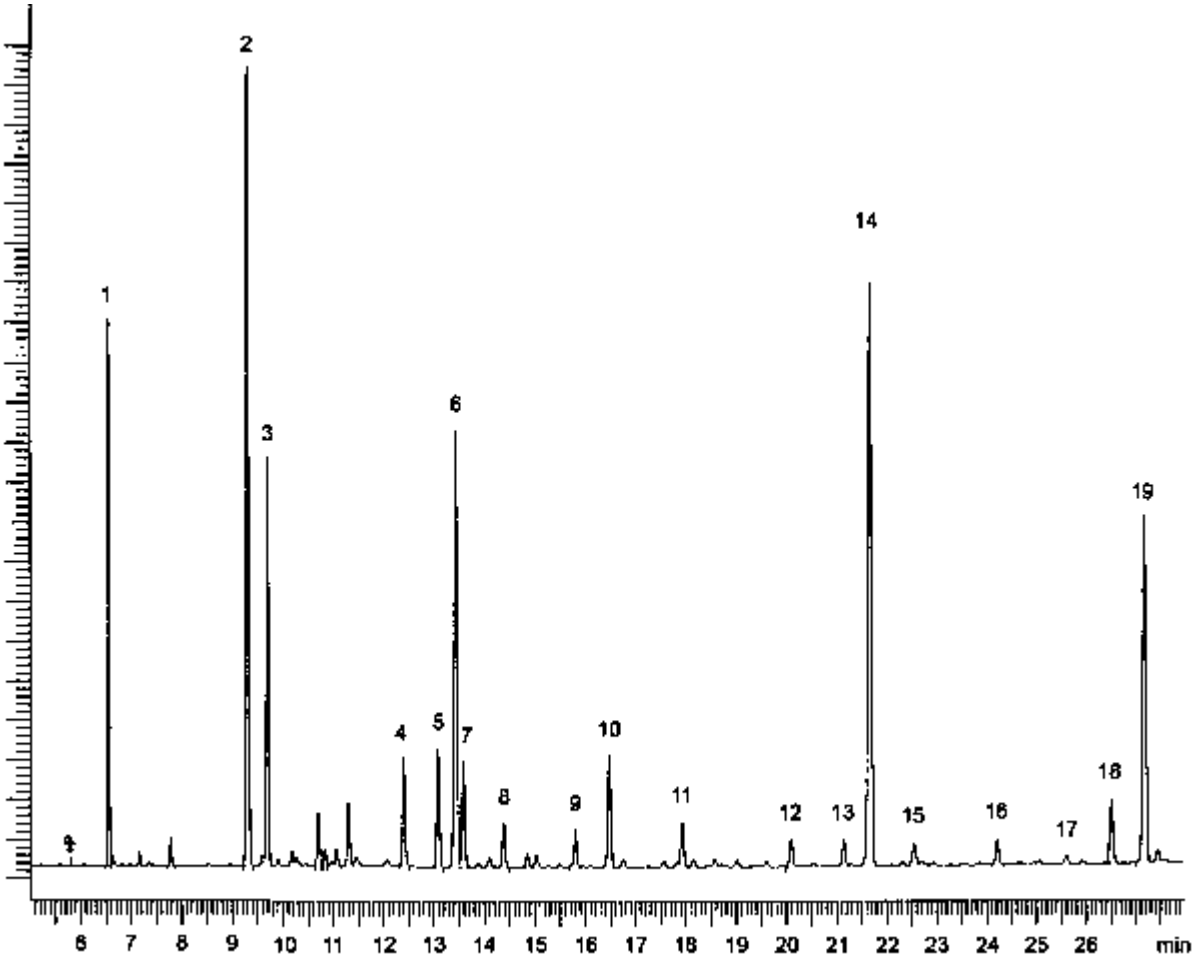
— *Lorentzian broadening factor*: 0.2 Hz.

Use the $CDCl_3$ signal for shift referencing. The shift of the central peak of the 1:1:1 triplet is set to 77.16 ppm.

Plot the spectral region δ 171.5-173.5 ppm. Compare the spectrum with the reference spectrum in Figure 1910.-2. The shift values lie within the ranges given in Table 1910.-1.

www.webofpharma.com

https://thuocngocanh.com/



1. C14:0	5. C18:0	9. C18:3 n-3	13. C20:4 n-3	17. C22:5 n-6
2. C16:0	6. C18:1 n-9	10. C18:4 n-3	14. EPA	18. C22:5 n-3
3. C16:1 n-7	7. C18:1 n-7	11. C20:1 n-9	15. C22:1 n-11	19. DHA
4. C16:4 n-1	8. C18:2 n-6	12. C20:4 n-6	16. C21:5 n-3	

Figure 1910.-1. – *Chromatogram for the composition of fatty acids in farmed salmon oil*

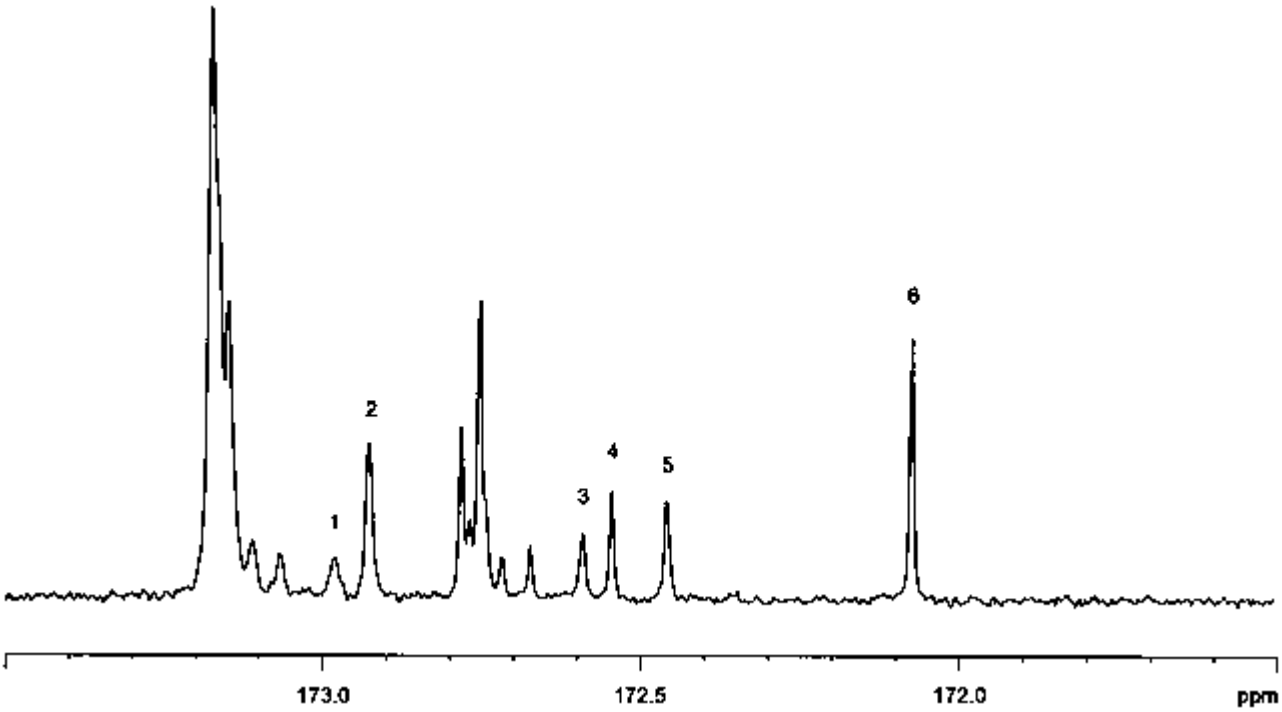
Table 1910.-1. – *Shift values*

Signal	Shift range (ppm)
β DHA	172.05 - 172.09
α DHA	172.43 - 172.47
β EPA	172.52 - 172.56
α EPA	172.90 - 172.94

www.webofpharma.com

https://thuocngocanh.com/

Signal	Shift range (ppm)
β C18:4	172.56 - 172.60
α C18:4	172.95 - 172.99



1. α C18:4 2. α EPA 3. β C18:4 4. β EPA 5. α DHA 6. β DHA

Figure 1910.-2. – *^{13}C NMR spectrum: carbonyl region of farmed salmon oil*

System suitability:

— *signal-to-noise ratio*: minimum 5 for the smallest relevant peak corresponding to α C18:4 signal (in the range δ 172.95-172.99 ppm);

— *peak width at half-height* maximum 0.02 ppm for the central $CDCl_3$ signal (at δ 77.16 ppm).

Calculation of positional distribution (β(2)-acyl) Use the following expression:

$$\frac{\beta}{\alpha+\beta} \times 100$$

α = peak area of the corresponding α-carbonyl peak;

β = peak area of β-carbonyl peak from C22:6 n-3, C20:5 n-3 or C18:4 n-3, respectively.

Limits:

— *cervonic (docosahexaenoic) acid (C22:6 n-3; DHA)*: 60 per cent to 70 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA)*: 25 per cent to 35 per cent;

— *moroctic acid (C18:4 n-3)*: 40 per cent to 55 per cent.

EPA and DHA (2.4.29)

See Figure 1910.-1.

STORAGE

In an airtight, well-filled container, protected from light, under inert gas.

LABELLING

The label states:

— the concentration of EPA and DHA, expressed as triglycerides.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

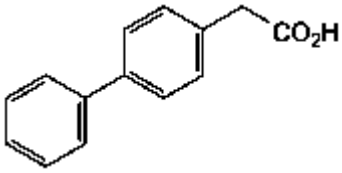
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Felbinac

General Notices

(Ph. Eur. monograph 2304)



$C_{14}H_{12}O_2$ 212.2 *5728-52-9*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

(Biphenyl-4-yl)acetic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent).

mp

About 164 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *felbinac CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Protect the solutions from light and inject within 20 min of preparation.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 5.0 mg of *felbinac impurity A CRS* and 5.0 mg of *biphenyl R* (impurity B) in *methanol R*, add 0.5 mL of the test solution and dilute to 50.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 45 volumes of a 0.1 per cent *V/V* solution of *glacial acetic acid R* and 55 volumes of *methanol R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 3.5 times the retention time of felbinac.

Relative retention With reference to felbinac (retention time = about 15 min): impurity A = about 1.3; impurity B = about 2.8.

System suitability Reference solution:

— *resolution*: minimum 3.0 between the peaks due to felbinac and impurity A.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent);

— *impurity B*: not more than the area of the peak due to felbinac in the chromatogram obtained with the reference solution (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to felbinac in the chromatogram obtained with the reference solution (0.10 per cent);

— *total*: not more than twice the area of the peak due to felbinac in the chromatogram obtained with the reference solution (0.2 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.5 times the area of the peak due to felbinac in the chromatogram obtained with the reference solution (0.05 per cent).

Chlorides

Maximum 110 ppm.

Dissolve 1.0 g in 40 mL of *acetone R*, add 6 mL of a 10 per cent *V/V* solution of *nitric acid R*, dilute to 50.0 mL with *water R* and mix. Pour 15.0 mL of this solution as a single addition into 1 mL of *0.1 M silver nitrate* and allow to stand for 5 min protected from light. When viewed horizontally against a black background, any opalescence produced is not more intense than that obtained by treating in the same manner 15.0 mL of a mixture of 1.5 mL of *0.002 M hydrochloric acid*, 40 mL of *acetone R*, 6 mL of 10 per cent *V/V* solution of *nitric acid R*, diluted to 50.0 mL with *water R*.

Sulfates

Maximum 130 ppm.

Dissolve 1.5 g in 40 mL of *dimethylformamide R*, add 1 mL of a 10 per cent *V/V* solution of *hydrochloric acid R*, dilute to 50.0 mL with *dimethylformamide R* and mix. To 15.0 mL of this solution add 2.0 mL of a 120 g/L solution of *barium chloride R* and allow to stand for 5 min. Any opalescence produced is not more intense than that of a standard prepared in the same manner but using 2.0 mL of *0.001 M sulfuric acid* instead of the substance to be examined.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.160 g in 50 mL of *methanol R*. Titrate with *0.1 M alcoholic potassium hydroxide* determining the end-point potentiometrically (*2.2.20*).

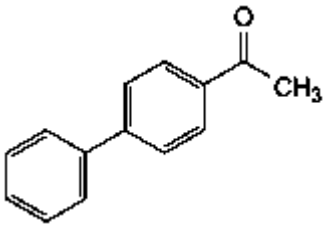
1 mL of *0.1 M alcoholic potassium hydroxide* is equivalent to 21.23 mg of $C_{14}H_{12}O_2$.

IMPURITIES

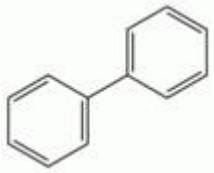
Specified impurities *A, B.*

www.webofpharma.com

https://thuocngocanh.com/



A. 4-acetyl biphenyl,



B. biphenyl.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Felbinac Cutaneous Foam

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Felbinac Cutaneous Foam is a fluid foam containing Felbinac in solution in a suitable pressurised container.

The cutaneous foam complies with the requirements stated under Medicated Foams and with the following requirements.

Content of felbinac, $C_{14}H_{12}O_2$

95.0 to 105.0% of the stated amount.

In each of the following tests, discharge a quantity of the foam into a suitable vessel with the can upright. Quantitatively transfer the foam using methanol. Determine the sample weight by difference.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dissolve a weighed quantity of the foam containing 60 mg of Felbinac in *methanol*, warming slightly if necessary to break the foam, and add sufficient *methanol* to produce 100 mL.

(2) 0.06% w/v solution of *felbinac BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable)

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 10 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)* (first examination). Spray the plate with a mixture of equal volumes of *formaldehyde solution* and *sulfuric acid* and heat at 110° for 10 minutes (second examination).

MOBILE PHASE

1 volume of *glacial acetic acid*, 25 volumes of *acetone* and 50 volumes of *hexane*.

CONFIRMATION

In the first examination:

www.webofpharma.com

https://thuocngocanh.com/

the principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

In the second examination:

the principal spots in the chromatograms obtained with solutions (1) and (2) are an intense purple colour.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH of the foam, 7.0 to 8.6, Appendix V L. Ensure good contact between the foam and the electrode.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a weighed quantity of the foam containing 30 mg of Felbinac in *methanol*, warming slightly if necessary to break the foam, and add sufficient *methanol* to produce 50 mL.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of this solution to 10 volumes with the same solvent.
(3) 0.00006% w/v of *4-acetylbiphenyl* and 0.00006% w/v of *biphenyl* in *methanol*.
(4) 0.001% w/v of *felbinac BPCRS* and 0.001% w/v of o-*phenylbenzoic acid* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Partisil ODS3 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 50 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for at least twice the retention time of the principal peak.

MOBILE PHASE

45 volumes of a 0.1% v/v solution of *glacial acetic acid* and 55 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the two principal peaks is at least 3.0.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-acetylbiphenyl is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any peak corresponding to biphenyl is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a weighed quantity of the foam containing 30 mg of felbinac in 60 mL of *methanol*, warming slightly, if necessary, to break the foam, add slowly, and with mixing, sufficient *water* to produce 100 mL and dilute 1 volume of the resulting solution to 20 volumes with the mobile phase.

(2) 0.0015% w/v of *felbinac BPCRS* in the mobile phase.

(3) 0.0015% w/v each of *felbinac BPCRS* and o-*phenylbenzoic acid* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under Related substances, with the exception of the run time. Inject 20 µL of each solution.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{12}O_2$ in the foam using the declared content of $C_{14}H_{12}O_2$ in *felbinac BPCRS*.

STORAGE

Felbinac Cutaneous Foam should be kept protected from light. It should not be refrigerated.

© Crown Copyright 2022

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://nhathuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Felbinac Gel

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; antinflammatory.

DEFINITION

Felbinac Gel is a solution of Felbinac in a suitable water-miscible basis.

The gel complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of felbinac, $C_{14}H_{12}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the gel containing 30 mg of Felbinac with sufficient *acetone* to produce 5 mL and mix.

(2) 0.6% w/v solution of *felbinac BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)* (first examination). Spray the plate with a mixture of equal volumes of *formaldehyde solution* and *sulfuric acid* and heat at 110° for 10 minutes (second examination).

MOBILE PHASE

1 volume of *glacial acetic acid*, 25 volumes of *acetone* and 50 volumes of *hexane*.

CONFIRMATION

In the first examination:

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

In the second examination:

The principal spots in the chromatograms obtained with solutions (1) and (2) are an intense purple colour.

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 7.0 to 8.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a weighed quantity of the gel containing 30 mg of Felbinac in *methanol* and add sufficient *methanol* to produce 50 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase and further dilute 1 volume of this solution to 10 volumes with the same solvent.

(3) 0.00006% w/v of *4-acetylbiphenyl* and 0.00006% w/v of *biphenyl* in *methanol*

(4) 0.001% w/v of *felbinac BPCRS* and 0.001% w/v of o-*phenylbenzoic acid* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Partisil ODS3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for at least twice the retention time of the principal peak.

MOBILE PHASE

45 volumes of a 0.1% v/v solution of *glacial acetic acid* and 55 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-acetylbiphenyl is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any peak corresponding to biphenyl is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the gel containing 30 mg of Felbinac in 70 mL of mobile phase, add sufficient mobile phase to produce 100 mL, mix and dilute 1 volume of the resulting solution to 20 volumes with mobile phase.

(2) 0.0015% w/v of *felbinac BPCRS* in mobile phase.

(3) 0.0015% w/v of *felbinac BPCRS* and 0.0015% w/v of o-*phenylbenzoic acid* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under Related substances, with the exception of the run time. Inject 20 µL of each solution.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{12}O_2$ in the gel from the chromatograms obtained using the declared content of $C_{14}H_{12}O_2$ in *felbinac BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

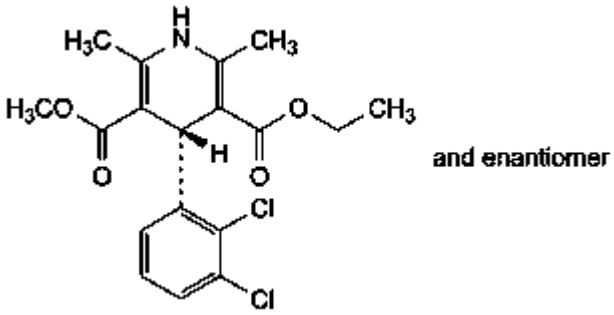
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Felodipine

General Notices

(Ph. Eur. monograph 1013)



and enantiomer

$C_{18}H_{19}Cl_2NO_4$ 384.3 *72509-76-3*

Action and use

Calcium channel blocker.

Preparation

Felodipine Prolonged-release Tablets

Ph Eur

DEFINITION

3-Ethyl 5-methyl (4*RS*)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or light yellow, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, freely soluble in anhydrous ethanol, in methanol and in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50 mg in methanol R and dilute to 100 mL with the same solvent. Dilute 3 mL of the solution to 100 mL with methanol R.

Spectral range 220-400 nm.

Absorption maxima 238 nm and 361 nm.

Absorbance ratio A_{361} / A_{238} = 0.34 to 0.36.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.250 g in a mixture of 40 mL of 2-methyl-2-propanol R and 25 mL of perchloric acid solution R. Add 20 mL of 0.1 M cerium sulfate, allow to stand for 15 min, add 6 mL of strong sodium hydroxide solution R and neutralise with dilute sodium hydroxide solution R. Shake with 50 mL of methylene chloride R. Evaporate the lower layer to dryness on a water-bath under nitrogen (the residue is also used in the test for related substances). Dissolve about 20 mg of the residue in methanol R and dilute to 50 mL with the same solvent. Dilute 2 mL of this solution to 50 mL with methanol R.

Spectral range 220-400 nm.

Absorption maximum 273 nm.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison felodipine CRS.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of felodipine CRS in methanol R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of nifedipine CRS in reference solution (a) and dilute to 5 mL with reference solution (a).

Plate TLC silica gel F_{254} plate R.

Mobile phase ethyl acetate R, cyclohexane R (40:60 *V/V*).

Application 5 µL.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, fluorescence and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 1.00 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*).

Absorbance (*2.2.25*)

Maximum 0.10, determined at 440 nm on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 50 mg of the residue obtained in identification test B (impurity A) and 25 mg of *felodipine CRS* in the mobile phase, then dilute to 50 mL with the mobile phase. Dilute 1 mL of the solution to 100 mL with the mobile phase. Dilute 1 mL of this solution to 10 mL with the mobile phase.

Reference solution (c) Dissolve 5 mg of *felodipine for peak identification CRS* (containing impurities B and C) in the mobile phase and dilute to 10 mL with the mobile phase.

Column:

— *size*: *l* = 0.125 m, Ø = 4 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 20 volumes of *methanol R*, 40 volumes of *acetonitrile R* and 40 volumes of a phosphate buffer solution pH 3.0 containing 0.8 g/L of *phosphoric acid R* and 8 g/L of *sodium dihydrogen phosphate R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time Twice the retention time of felodipine.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram supplied with *felodipine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B and C.

Relative retention With reference to felodipine (retention time = about 6 min): impurity B = about 0.7; impurity A = about 0.9; impurity C = about 1.4.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity A and felodipine.

Calculation of percentage contents:

— for each impurity, use the concentration of felodipine in reference solution (a).

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurity C*: maximum 0.5 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.160 g in a mixture of 25 mL of *2-methyl-2-propanol R* and 25 mL of *perchloric acid solution R*. Add 0.05 mL of *ferroin R*. Titrate with *0.1 M cerium sulfate* until the pink colour disappears. Titrate slowly towards the end of the titration.

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *0.1 M cerium sulfate* is equivalent to 19.21 mg of $C_{18}H_{19}Cl_2NO_4$.

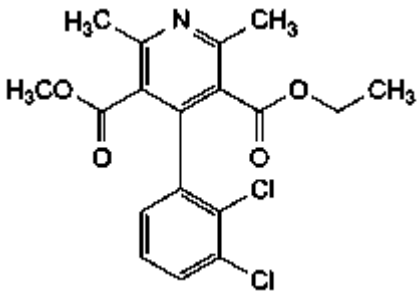
STORAGE

Protected from light.

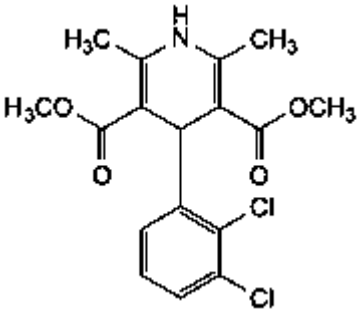
IMPURITIES

Specified impurities B, C.

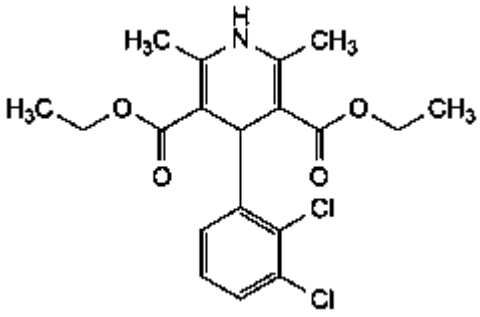
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



A. ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate,



B. dimethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate,



C. diethyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Felodipine Prolonged-release Tablets

General Notices

Prolonged-release Felodipine Tablets

Felodipine Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Calcium channel blocker.

DEFINITION

Felodipine Prolonged-release Tablets contain Felodipine. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Felodipine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of felodipine, $C_{18}H_{19}Cl_2NO_4$

92.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 15 mg of Felodipine with 100 mL of *ethanol (96%)*, filter, and dilute 5 mL of the filtrate to 50 mL with *ethanol (96%)*. The *light absorption*, Appendix II B, in the range 250 to 450 nm exhibits a maximum at 362 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 10 mg of Felodipine with 10 mL of *methanol* and filter through a 0.45-µm filter.

(2) 0.1% w/v of *felodipine BPCRS* in *methanol*.

(3) 0.1% w/v each of *felodipine BPCRS* and *nifedipine BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating substance *silica gel* F_{254}.

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

(d) Develop to 15 cm.

(e) Dry the plate in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

40 volumes of *ethyl acetate* and 60 volumes of *cyclohexane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots of different colours.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

C. In the Assay, the chromatogram obtained with solution (1) shows a principal peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Prepare a mixture of 0.08% w/v of *orthophosphoric acid R* and 0.8% w/v of *sodium dihydrogen orthophosphate* (solvent A).

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 10 mg of Felodipine with 10 mL of *methanol* and 20 mL of *acetonitrile* for 5 minutes, add 15 mL of solvent A and continue to disperse with the aid of ultrasound for a further 30 minutes. Cool, dilute to 50 mL with solvent A and filter through a 0.45-µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

(4) 0.006% w/v of *felodipine impurity standard BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Nova-Pak is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *methanol*, 40 volumes of *acetonitrile* and 40 volumes of solvent A.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to felodipine (retention time about 7 minutes) are: impurity B, about 0.7; impurity A, about 0.9; impurity C, about 1.4.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity A and felodipine is at least than 2.5.

LIMITS

Identify any peaks corresponding to impurities A, B and C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of the peak due to impurity A by a correction factor of 2.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to Impurity A is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%);

the sum of the areas of the peaks corresponding to impurity B and impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Prepare a mixture of 0.08% w/v of *orthophosphoric acid R* and 0.8% w/v of *sodium dihydrogen orthophosphate* (solvent A).

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 10 mg of Felodipine with 10 mL of methanol and 20 mL of *acetonitrile* for 5 minutes, add 15 mL of solvent A and mix with the aid of ultrasound for a further 30 minutes. Cool, add sufficient solvent A to produce 50 mL and filter through a 0.45-µm PTFE filter. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(2) 0.002% w/v of *felodipine BPCRS* in mobile phase.
(3) 0.006% w/v of *felodipine impurity standard BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and felodipine is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{18}H_{19}Cl_2NO_4$ in the tablets using the declared content of $C_{18}H_{19}Cl_2NO_4$ in *felodipine BPCRS*.

IMPURITIES

www.webofpharma.com

https://thuathuocngocanh.com/

The impurities limited by the requirements of this monograph include those impurities listed under Felodipine.

© Crown Copyright 2022

www.webofpharma.com

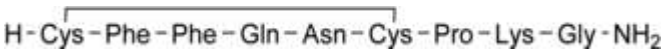
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Felypressin

General Notices

(Ph. Eur. monograph 1634)



$C_{46}H_{65}N_{13}O_{11}S_2$ 1039 *56-59-7*

Action and use

Vasopressin analogue; vasoconstrictor in local anaesthesia.

Ph Eur

DEFINITION

L-Cysteinyl-L-phenylalanyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-lysylglycinamide cyclic (1,6)-disulfide.

Synthetic nonapeptide having a vasoconstricting activity. It is available as an acetate.

Content

95.0 per cent to 102.0 per cent (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance

White or almost white, powder or flakes.

Solubility

Freely soluble in water, practically insoluble in acetone and ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

B. Amino acid analysis (*2.2.56*). For hydrolysis use Method 1 and for analysis use Method 1.

www.webofpharma.com

https://thuocngocanh.com/

Express the content of each amino acid in moles. Calculate the relative proportions of amino acids, taking one-seventh of the sum of the number of moles of glutamic acid, aspartic acid, proline, lysine, glycine and phenylalanine as equal to one. The values fall within the following limits: aspartic acid: 0.9 to 1.1; glutamic acid: 0.9 to 1.1; proline: 0.9 to 1.1; glycine: 0.9 to 1.1; phenylalanine: 1.8 to 2.2; half-cystine: 1.8 to 2.2; lysine: 0.9 to 1.1.

TESTS

Specific optical rotation (2.2.7)

-35 to -29, determined at 25 °C (anhydrous and acetic acid-free substance).

Dissolve 20.0 mg in a 1 per cent *V/V* solution of *glacial acetic acid R* and dilute to 10.0 mL with the same solution.

Related substances

Liquid chromatography (2.2.29); use the normalisation procedure. *The solutions are stable for 24 h at room temperature or for 1 week at 2-8 °C.*

Test solution (a) Dissolve 5.0 mg of the substance to be examined in 5.0 mL of mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 5.0 mL with mobile phase A.

Reference solution Dissolve the contents of a vial of *felypressin CRS* in mobile phase A to obtain a concentration of 0.2 mg/mL.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: dissolve 3.62 g of *tetramethylammonium hydroxide R* in 900 mL *water R*; adjust to pH 2.5 with *phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: dissolve 1.81 g of *tetramethylammonium hydroxide R* in 450 mL of a 50 per cent *V/V* solution of *acetonitrile for chromatography R*; adjust to pH 2.5 with *phosphoric acid R* and dilute to 500 mL with a 50 per cent *V/V* solution of *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	80 → 50	20 → 50
20 - 25	50	50

Flow rate 1.0 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 210 nm.

Injection 10 µL of test solution (a) and 50 µL of the reference solution.

Identification of impurities Use the chromatogram supplied with *felypressin CRS* to identify the peaks due to impurities A to F.

Relative retention With reference to felypressin: impurity A = about 0.9; impurity B = about 1.1; impurity F = about 1.2; impurity C = about 1.3; impurity D = about 1.4; impurity E = about 2.1.

System suitability Reference solution:

— *retention time*: felypressin = about 7.5 min;

— *resolution*: minimum 1.5 between the peaks due to impurity C and impurity D.

Limits:

— *impurities A, B, C, D, E, F*: for each impurity, maximum 0.5 per cent,

— *any other impurity*: for each impurity, maximum 0.1 per cent,

— *total*: maximum 3.0 per cent,

— *disregard limit*: 0.05 per cent.

Acetic acid (*2.5.34*)

9.0 per cent to 13.0 per cent.

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of mobile phases.

Water (*2.5.32*)

Maximum 7.0 per cent.

Bacterial endotoxins (*2.6.14*)

Less than 100 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 10 µL of test solution (b) and of the reference solution.

Calculate the content of felypressin ($C_{46}H_{65}N_{13}O_{11}S_2$) from the areas of the peaks and the declared content of $C_{46}H_{65}N_{13}O_{11}S_2$ in *felypressin CRS*.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

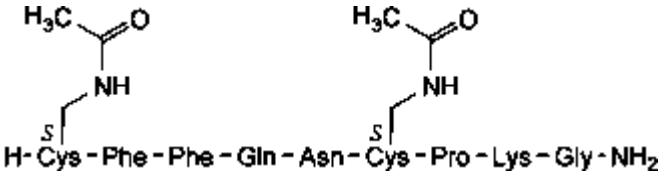
In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

LABELLING

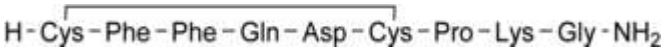
The label states the mass of peptide in the container.

IMPURITIES

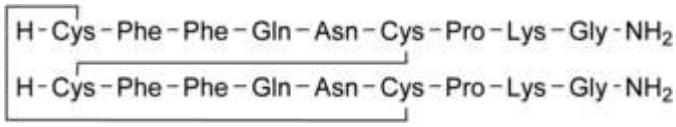
Specified impurities *A, B, C, D, E, F.*



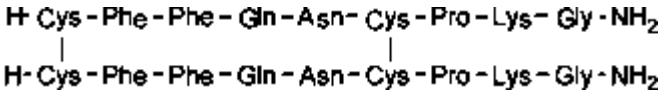
A. S^1,S^6-bis[(acetylamino)methyl]-(reduced felypressin),



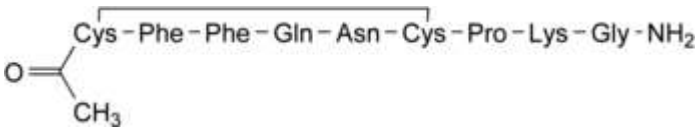
B. [5-aspartic acid]felypressin,



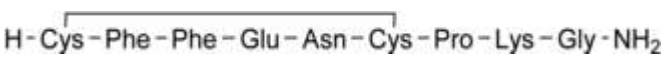
C. bis(reduced felypressin) (1,6′),(1′,6)-bis(disulfide),



D. bis(reduced felypressin) (1,1′),(6,6′)-bis(disulfide),



E. N^1-acetylfelypressin,



F. [4-glutamic acid]felypressin.

www.webofpharma.com

https://thuocngocanh.com/

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

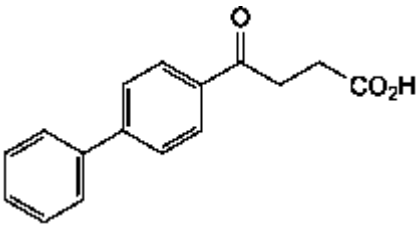
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fenbufen

General Notices

(Ph. Eur. monograph 1209)



$C_{16}H_{14}O_3$ 254.3 *36330-85-5*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Ph Eur

DEFINITION

4-(Biphenyl-4-yl)-4-oxobutanoic acid.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, fine, crystalline powder.

Solubility

Very slightly soluble in water, slightly soluble in acetone, in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: B.

Second identification: A, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 186 °C to 189 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison fenbufen CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methylene chloride R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of fenbufen CRS in methylene chloride R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of ketoprofen CRS in methylene chloride R and dilute to 10 mL with the same solvent. To 5 mL of this solution, add 5 mL of reference solution (a).

Plate TLC silica gel F_{254} plate R.

Mobile phase anhydrous acetic acid R, ethyl acetate R, hexane R (5:25:75 *V/V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture dimethylformamide R, mobile phase A (40:60 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 0.5 mL of the test solution to 50.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 25 mg of fenbufen CRS and 6 mg of ketoprofen CRS in the solvent mixture and dilute to 10 mL with the solvent mixture. Dilute 1 mL of this solution to 100 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 32 volumes of *acetonitrile R* and 68 volumes of a mixture of 1 volume of *glacial acetic acid R* and 55 volumes of *water R*;

— *mobile phase B*: mix 45 volumes of *acetonitrile R* and 55 volumes of a mixture of 1 volume of *glacial acetic acid R* and 55 volumes of *water R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 – 15	100	0
15 – 20	100 → 0	0 → 100
20 – 35	0	100

Flow rate 2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to ketoprofen and fenbufen.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

www.webofpharma.com

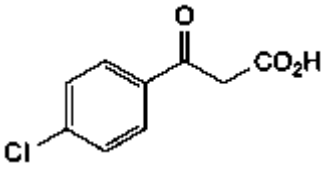
https://thuvienthuocngocanh.com/

ASSAY

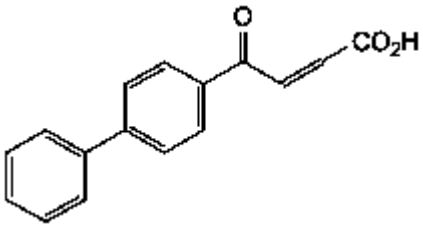
Dissolve 0.200 g in 75 mL of *acetone R* previously neutralised with *phenolphthalein solution R1* and add 50 mL of *water R*. Add 0.2 mL of *phenolphthalein solution R1* and titrate with *0.1 M sodium hydroxide*. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 25.43 mg of $C_{16}H_{14}O_3$.

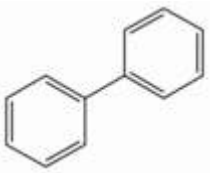
IMPURITIES



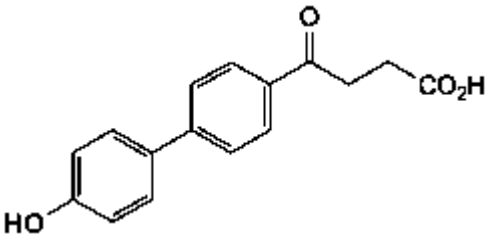
A. 3-(4-chlorophenyl)-3-oxopropanoic acid,



B. 4-(biphenyl-4-yl)-4-oxobut-2-enoic acid,



C. biphenyl,



D. 4-(4′-hydroxybiphenyl-4-yl)-4-oxobutanoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

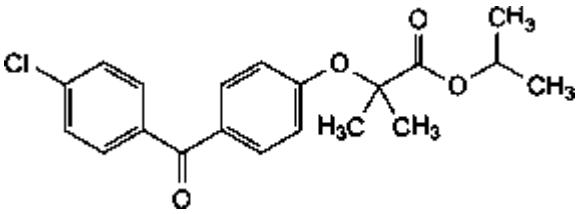
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fenofibrate

General Notices

(Ph. Eur. monograph 1322)



$C_{20}H_{21}ClO_4$ 360.8 *49562-28-9*

Action and use

Fibrate; lipid-regulating drug.

Ph Eur

DEFINITION

1-Methylethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 79 °C to 82 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *fenofibrate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

To 5.0 g, add 25 mL of *distilled water R* and heat at 50 °C for 10 min. Cool and dilute to 50.0 mL with *distilled water R*. Filter. Use the filtrate as solution S.

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 0.50 g in *acetone R* and dilute to 10.0 mL with the same solvent.

Acidity

Dissolve 1.0 g in 50 mL of *ethanol (96 per cent) R* previously neutralised using 0.2 mL of *phenolphthalein solution R1*. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *fenofibrate CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *fenofibrate CRS*, 5.0 mg of *fenofibrate impurity A CRS*, 5.0 mg of *fenofibrate impurity B CRS* and 10.0 mg of *fenofibrate impurity G CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 30 volumes of *water R* acidified to pH 2.5 with *phosphoric acid R* and 70 volumes of *acetonitrile R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 286 nm.

Injection 20 µL of the test solution and reference solution (b).

Run time Twice the retention time of fenofibrate.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and G.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to fenofibrate (retention time = about 10 min): impurity A = about 0.34; impurity B = about 0.36; impurity G = about 1.35.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B.

Limits:

— *impurities A, B*: for each impurity, not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurity G*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to fenofibrate in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the peak due to fenofibrate in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the peak due to fenofibrate in the chromatogram obtained with reference solution (b) (0.05 per cent).

Halides expressed as chlorides (2.4.4)

Maximum 100 ppm.

To 5 mL of solution S add 10 mL of *distilled water R*.

Sulfates (2.4.13)

Maximum 100 ppm, determined on solution S.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection 5 µL of the test solution and reference solution (a).

System suitability Reference solution (a):

www.webofpharma.com

https://thuocngocanh.com/

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

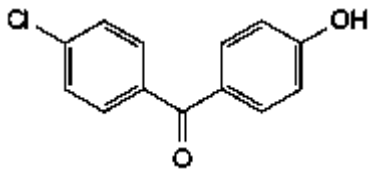
STORAGE

Protected from light.

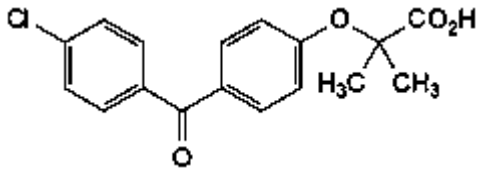
IMPURITIES

Specified impurities *A, B, G.*

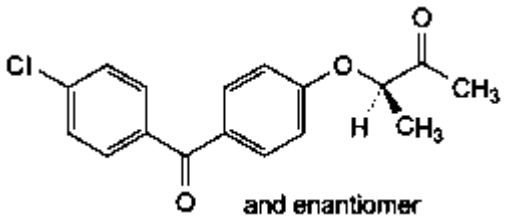
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E, F.*



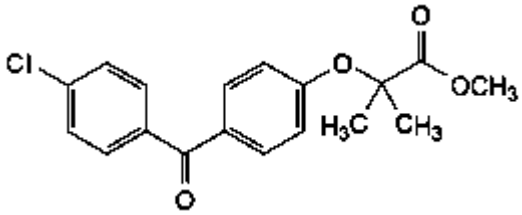
A. (4-chlorophenyl)(4-hydroxyphenyl)methanone,



B. 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid (fenofibric acid),



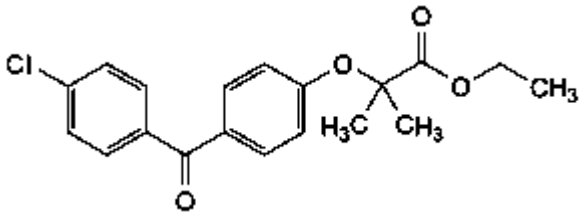
C. (3*RS*)-3-[4-(4-chlorobenzoyl)phenoxy]butan-2-one,



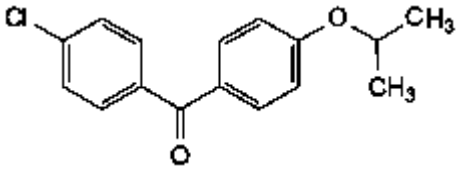
D. methyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate,

www.webofpharma.com

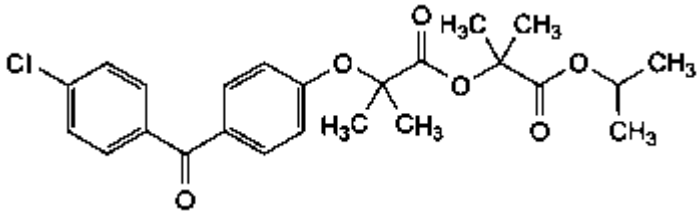
https://thuocngocanh.com/



E. ethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate,



F. (4-chlorophenyl)[4-(1-methylethoxy)phenyl]methanone,



G. 1-methylethyl 2-[[2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoyl]oxy]-2-methylpropanoate.

Ph Eur

© Crown Copyright 2022

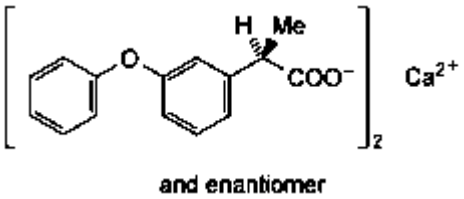
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fenoprofen Calcium

General Notices



and enantiomer

$(C_{15}H_{13}O_3)_2Ca,2H_2O$ 558.6 *34957-40-5*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparation

Fenoprofen Tablets

DEFINITION

Fenoprofen Calcium is calcium (*RS*)-2-(3-phenoxyphenyl)propionate dihydrate. It contains not less than 97.5% and not more than 101.0% of $(C_{15}H_{13}O_3)_2Ca$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white or almost white, crystalline powder.

Slightly soluble in *water*; soluble in *ethanol (96%)*.

IDENTIFICATION

A. Dissolve 0.1 g in 5 mL of *glacial acetic acid* and add sufficient *methanol* to produce 100 mL. Dilute 5 mL of this solution to 50 mL with *methanol*. The *light absorption* of the resulting solution, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 272 nm and 278 nm, and a shoulder at 266 nm. The *absorbance* at the maximum at 272 nm is about 0.70 and at the maximum at 278 nm is about 0.65.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of fenoprofen calcium *(RS 142)*.

C. The residue on ignition yields the reactions characteristic of *calcium salts*, Appendix VI.

TESTS

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase.

(1) 0.50% w/v of the substance being examined.

(2) 0.0025% w/v of the substance being examined.

(3) 0.04% w/v of *fenoprofen calcium* and 0.0015% w/v of *4,4'-dimethoxybenzophenone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (7 to 8 µm) (Zorbax ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of the peak due to fenoprofen.

MOBILE PHASE

2 volumes of *glacial acetic acid*, 7 volumes of *tetrahydrofuran*, 30 volumes of *acetonitrile* and 61 volumes of *water*.

SYSTEM SUITABILITY

The test is valid if the *resolution factor* between the peaks corresponding to fenoprofen and 4,4′-dimethoxybenzophenone in the chromatogram obtained with solution (3) is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (1%);

not more than one *secondary peak* has an area greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than four times the area of the peak in the chromatogram obtained with solution (2) (2%).

Water

5.0 to 8.0% w/w, Appendix IX C. Use 0.2 g.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.5 g and determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 26.13 mg of $(C_{15}H_{13}O_3)_2Ca$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fenoprofen Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Fenoprofen Tablets contain Fenoprofen Calcium. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of fenoprofen, $C_{15}H_{14}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits two maxima, at 272 nm and 278 nm, and a shoulder at 266 nm.

B. Suspend a quantity of the powdered tablets containing the equivalent of 0.3 g of fenoprofen in 10 mL of 0.1M *hydrochloric acid*. Extract with 20 mL of *chloroform*, filter the extract through *anhydrous sodium sulfate* and evaporate the filtrate to dryness. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of fenoprofen *(RS 141)*.

C. Ignite a quantity of the powdered tablets. The residue yields the reactions characteristic *of calcium salts*, Appendix VI.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 0.5 g of fenoprofen add 80 mL of the mobile phase, mix with the aid of ultrasound, allow to cool, add sufficient mobile phase to produce 100 mL and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.04% w/v of *fenoprofen calcium* and 0.0015% w/v of *4,4'-dimethoxybenzophenone* in the mobile phase.

(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (7 to 8 µm) (Zorbax ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 3 times the retention time of the peak due to fenoprofen.

MOBILE PHASE

2 volumes of *glacial acetic acid*, 7 volumes of *tetrahydrofuran*, 30 volumes of *acetonitrile* and 61 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to fenoprofen calcium and 4′,4′-dimethoxybenzophenone is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (1.0%);

not more than one such peak has an area greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all such peaks is not greater than four times the area of the peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing the equivalent of 0.2 g of fenoprofen add 5 mL of *glacial acetic acid* and shake for 1 minute. Add 100 mL of *methanol*, shake for 5 minutes, dilute to 200 mL with *methanol* and filter. Dilute 10 mL of the filtrate to 200 mL with *methanol* and measure the *absorbance* of the resulting solution at the maximum at 272 nm, Appendix II B. Calculate the content of $C_{15}H_{14}O_3$ taking 80.7 as the value of A (1%, 1 cm) at the maximum at 272 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of fenoprofen.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

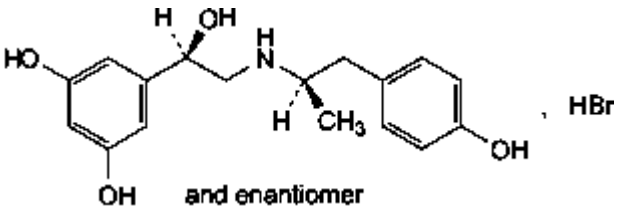
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fenoterol Hydrobromide

General Notices

(Ph. Eur. monograph 0901)



$C_{17}H_{22}BrNO_4$ 384.3 *1944-12-3*

Action and use

$Beta_2$-adrenoceptor agonist; bronchodilator.

Ph Eur

DEFINITION

5-[(1*RS*)-2-[(1*RS*)-2-(4-Hydroxyphenyl)-1-methylethyl]amino-1-hydroxyethyl]benzene-1,3-diol hydrobromide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *fenoterol hydrobromide CRS*.

B. It gives reaction (a) of bromides (2.3.1).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 2.00 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*)

4.2 to 5.2 for solution S.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use*.

Test solution Dissolve 6.0 mg of the substance to be examined in *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 25.0 mL with *water R*.

Reference solution (b) Dilute 2.5 mL of reference solution (a) to 100.0 mL with *water R*.

Reference solution (c) Dissolve the contents of a vial of *fenoterol for system suitability CRS* (containing impurities A, B and C) in 1 mL of *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 24 g of *anhydrous disodium hydrogen phosphate R* in 1000 mL of *water for chromatography R*. Mix 69 volumes of the solution and 1 volume of a 9 g/L solution of *potassium dihydrogen phosphate R*, adjust to pH 8.5 with *phosphoric acid R* and add 35 volumes of *methanol R2*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 3 times the retention time of fenoterol.

Identification of impurities Use the chromatogram supplied with *fenoterol for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to fenoterol (retention time = about 7 min): impurity A = about 1.3; impurity B = about 2.0; impurity C = about 2.2.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to fenoterol and impurity A; minimum 1.5 between the peaks due to impurities B and C.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.6;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (4.0 per cent);

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *sum of impurities other than A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Iron (*2.4.9*)

Maximum 10 ppm.

Dissolve the residue obtained in the test for sulfated ash in 2.5 mL of *dilute hydrochloric acid R* and dilute to 10 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.600 g in 50 mL of *water R* and add 5 mL of *dilute nitric acid R*, 25.0 mL of *0.1 M silver nitrate* and 2 mL of *ferric ammonium sulfate solution R2*. Shake and titrate with *0.1 M ammonium thiocyanate* until an orange colour is obtained. Carry out a blank titration.

1 mL of *0.1 M silver nitrate* is equivalent to 38.43 mg of $C_{17}H_{22}BrNO_4$.

www.webofpharma.com

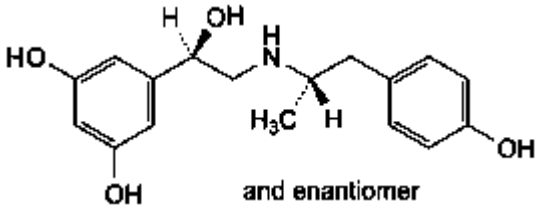
https://thuocngocanh.com/

STORAGE

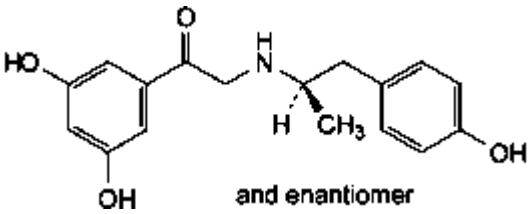
Protected from light.

IMPURITIES

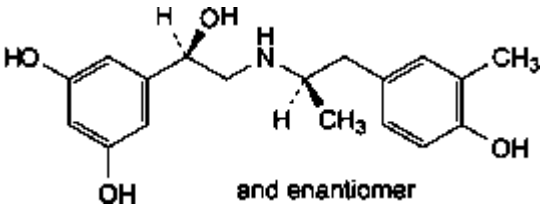
Specified impurities *A, B, C.*



A. 5-[(1*RS*)-2-[(1*SR*)-2-(4-hydroxyphenyl)-1-methylethyl]amino-1-hydroxyethyl]benzene-1,3-diol,



B. 1-(3,5-dihydroxyphenyl)-2-[[(1*RS*)-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethan-1-one,



C. 5-[(1*RS*)-2-[(1*RS*)-2-(4-hydroxy-3-methylphenyl)-1-methylethyl]amino-1-hydroxyethyl]benzene-1,3-diol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

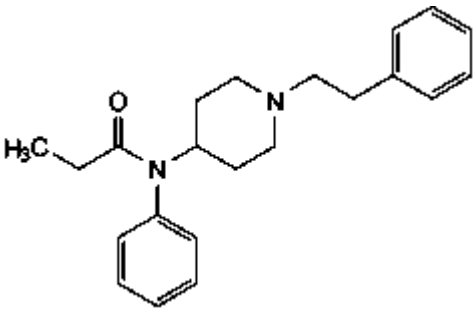
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fentanyl

General Notices

(Ph. Eur. monograph 1210)



$C_{22}H_{28}N_2O$ 336.5 *437-38-7*

Action and use

Opioid receptor agonist; analgesic.

Ph Eur

DEFINITION

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent), in methanol and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *fentanyl CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *anhydrous ethanol R*, evaporate to dryness at room temperature in a current of air and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *methanol R*, *water R* (50:50 *V/V*).

Test solution Dissolve 25 mg of the substance to be examined in 2.5 mL of *methanol R* and dilute to 5.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the solvent mixture. Dissolve the contents of a vial of *fentanyl impurity mixture CRS* (impurities C and D) in 1.0 mL of this solution, using sonication for 1 min if necessary.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.8 g of *ammonium acetate R* in *water for chromatography R*, add 2 mL of *trifluoroacetic acid R* and dilute to 1000.0 mL with *water for chromatography R*;

— *mobile phase B*: add 2 mL of *trifluoroacetic acid R* to 950 mL of *acetonitrile R1* and shake to homogenise; dissolve 0.8 g of *ammonium acetate R* in this solution and shake until complete dissolution, then dilute to 1000.0 mL with *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	98	2
1 - 5	98 → 90	2 → 10
5 - 17	90 → 70	10 → 30

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
17 - 30	70 → 5	30 → 95
30 - 31	5	95

Flow rate 0.35 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with *fentanyl impurity mixture CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and D.

Relative retention With reference to fentanyl (retention time = about 19 min): impurity D = about 0.8; impurity C = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity C and fentanyl.

Calculation of percentage contents:

— for each impurity, use the concentration of fentanyl in reference solution (b).

Limits:

— *impurities C, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 50 °C.

ASSAY

Dissolve 0.200 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 33.65 mg of $C_{22}H_{28}N_2O$.

STORAGE

www.webofpharma.com

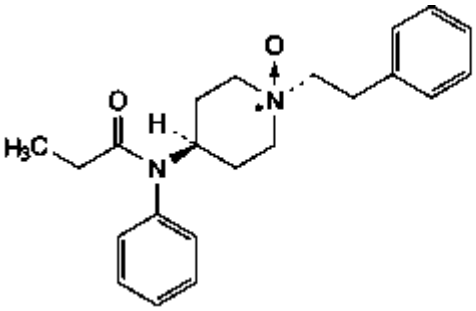
https://thuocngocanh.com/

Protected from light.

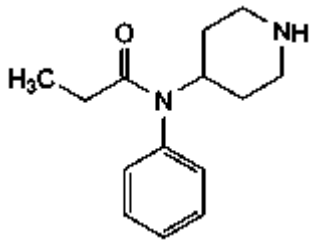
IMPURITIES

Specified impurities C, D.

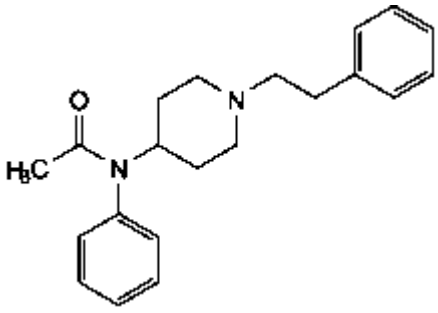
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, E, F, G, H, I, J, K, L.



A. (1*rs*,4*rs*)-1-(2-phenylethyl)-4-(*N*-phenylpropanamido)piperidine *N*-oxide,



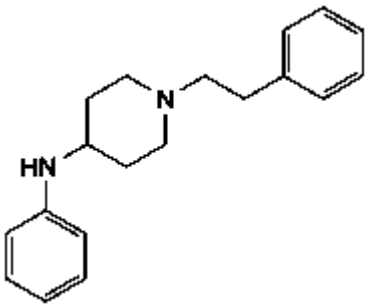
B. *N*-phenyl-*N*-(piperidin-4-yl)propanamide,



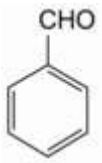
C. *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide,

www.webofpharma.com

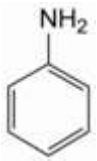
https://thuocngocanh.com/



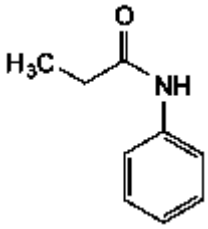
D. *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine,



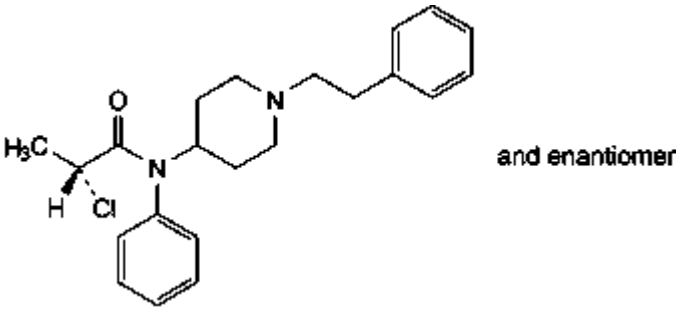
E. benzaldehyde,



F. aniline (phenylamine),



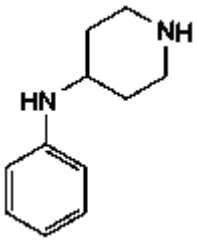
G. *N*-phenylpropanamide,



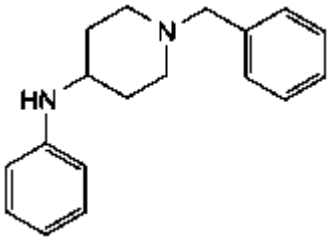
H. (2*RS*)-2-chloro-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide,

www.webofpharma.com

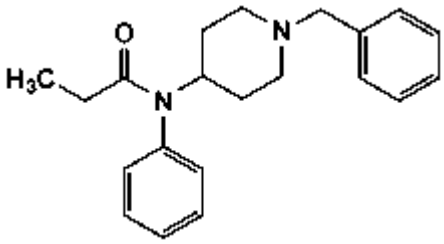
https://thuocngocanh.com/



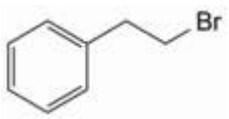
I. *N*-phenylpiperidin-4-amine,



J. 1-benzyl-*N*-phenylpiperidin-4-amine,



K. *N*-(1-benzylpiperidin-4-yl)-*N*-phenylpropanamide,



L. (2-bromoethyl)benzene.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

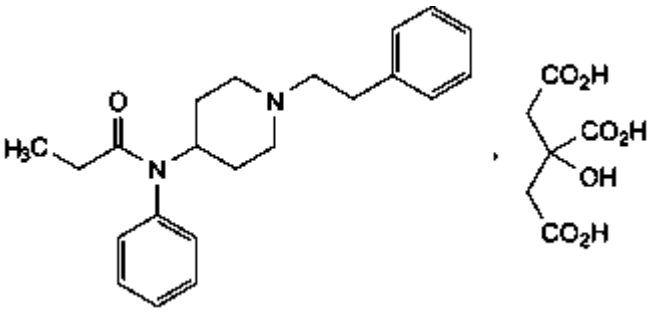
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fentanyl Citrate

General Notices

(Ph. Eur. monograph 1103)



$C_{28}H_{36}N_2O_8$ 528.6 *990-73-8*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Bupivacaine and Fentanyl Injection

Fentanyl Injection

Ph Eur

DEFINITION

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Soluble in water, freely soluble in methanol, sparingly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

mp

About 152 °C, with decomposition.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *fentanyl citrate CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.2 g of the substance to be examined in *water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *methanol R*, *water R* (50:50 *V/V*).

Test solution Dissolve 39.3 mg of the substance to be examined in 2.5 mL of *methanol R* and dilute to 5.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the solvent mixture. Dissolve the contents of a vial of *fentanyl impurity mixture CRS* (impurities C and D) in 1.0 mL of this solution, using sonication for 1 min if necessary.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (1.7 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.8 g of *ammonium acetate R* in *water for chromatography R*, add 2 mL of *trifluoroacetic acid R* and dilute to 1000.0 mL with *water for chromatography R*;

— *mobile phase B*: add 2 mL of *trifluoroacetic acid R* to 950 mL of *acetonitrile R1* and shake to homogenise; dissolve 0.8 g of *ammonium acetate R* in this solution and shake until complete dissolution, then dilute to 1000.0 mL with *acetonitrile R1*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 1	98	2
1 - 5	98 → 90	2 → 10
5 - 17	90 → 70	10 → 30
17 - 30	70 → 5	30 → 95
30 - 31	5	95

Flow rate 0.35 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with *fentanyl impurity mixture CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C and D.

Relative retention With reference to fentanyl (retention time = about 19 min): impurity D = about 0.8; impurity C = about 0.9.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity C and fentanyl.

Calculation of percentage contents:

— for each impurity, use the concentration of fentanyl citrate in reference solution (b).

Limits:

— *impurities C, D*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

ASSAY

Dissolve 0.300 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *0.1 M perchloric acid* is equivalent to 52.86 mg of $C_{28}H_{36}N_2O_8$.

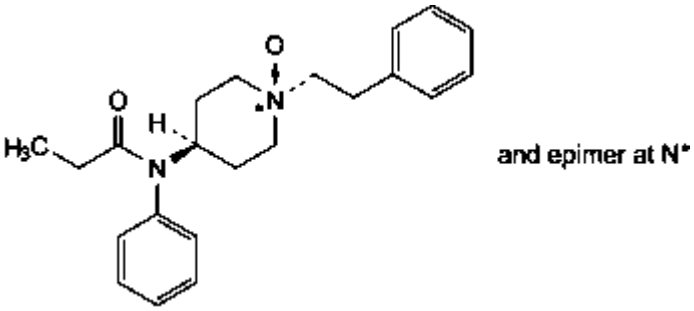
STORAGE

Protected from light.

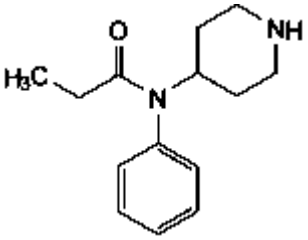
IMPURITIES

Specified impurities C, D.

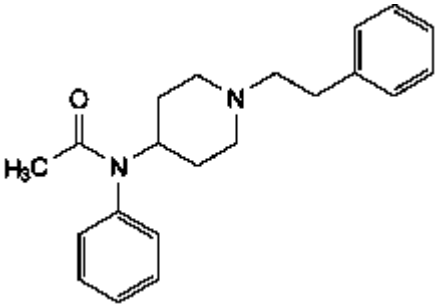
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, E, F, G, H, I.



A. (1*rs*,4*rs*)-1-(2-phenylethyl)-4-(*N*-phenylpropanamido)piperidine *N*-oxide,



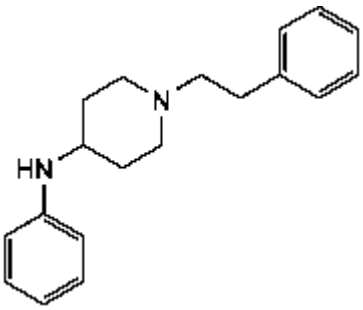
B. *N*-phenyl-*N*-(piperidin-4-yl)propanamide,



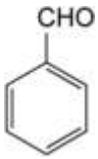
C. *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide,

www.webofpharma.com

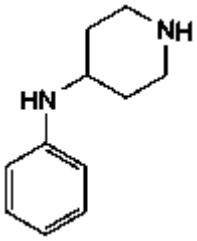
https://thuocngocanh.com/



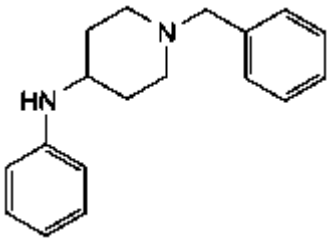
D. *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine,



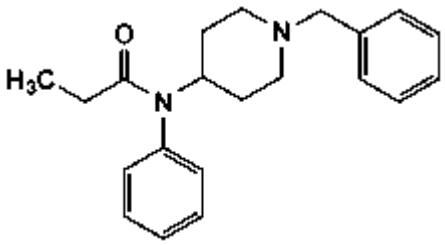
E. benzaldehyde,



F. *N*-phenylpiperidin-4-amine,



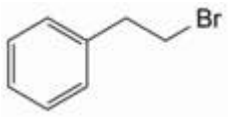
G. 1-benzyl-*N*-phenylpiperidin-4-amine,



H. *N*-(1-benzylpiperidin-4-yl)-*N*-phenylpropanamide,

www.webofpharma.com

https://thuocngocanh.com/



I. (2-bromoethyl)benzene.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fentanyl Injection

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Fentanyl Injection is a sterile solution of Fentanyl Citrate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of fentanyl, $C_{22}H_{28}N_2O$

95.0% to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the injection diluted, if necessary, to contain the equivalent of 0.005% w/v of fentanyl exhibits two maxima at 251 and 257 nm and a shoulder at 262 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) The injection being examined, diluted with the mobile phase if necessary, to contain the equivalent of 0.005% w/v of fentanyl.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 5 volumes of the resulting solution to 20 volumes with the mobile phase.

(3) Dissolve 5 mg of *fentanyl citrate BPCRS* in 9 mL of *water*, add 1 mL of *hydrogen peroxide solution (30 per cent)* and heat at 95° for 1 to 2 hours. Allow to cool and dilute to 25 mL with the mobile phase (generation of impurity A).

(4) Dissolve 5 mg of *fentanyl citrate BPCRS* in 10 mL of 2M *hydrochloric acid*, heat on a waterbath under a reflux condenser for 4 hours and neutralise with 10 mL of 2M *sodium hydroxide*. Evaporate to dryness on a waterbath, cool, dissolve the residue in 10 mL of *methanol* and filter. Dilute 1 volume of the filtrate to 5 volumes with the mobile phase (generation of impurity D).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Bondclone C18 10µ is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.25 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 100 µL of each solution. Inject *methanol* as a blank prior to the solutions.

(g) For solutions (1) and (2) allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

0.3% w/v of *potassium dihydrogen orthophosphate* in a mixture of 4 volumes of *acetonitrile*, 40 volumes of *methanol* and 56 volumes of *water*, the solution adjusted to pH 3.2 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative time of fentanyl is about 6 minutes and the relative retention of fentanyl impurity A is about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the retention time of fentanyl impurity D is about 0.8 relative to fentanyl.

LIMITS

Identify any peaks corresponding to impurities A and D in the chromatogram obtained with solution (1), using the chromatograms obtained with solutions (3) and (4) respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to fentanyl impurity A is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to fentanyl impurity D is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of any *secondary peaks* apart from any peaks corresponding to fentanyl impurity A and fentanyl impurity D is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%).

Disregard any peak obtained with the blank solution and any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) The injection diluted, if necessary, to contain the equivalent of 0.005% w/v of fentanyl.

(2) 0.008% w/v solution of *fentanyl citrate BPCRS*.

www.webofpharma.com

https://thietbiuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{28}N_2O$ in the injection using the declared content of $C_{22}H_{28}N_2O$ in *fentanyl citrate BPCRS*.

STORAGE

Fentanyl Injection should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of fentanyl.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A and impurity D listed under Fentanyl Citrate.

© Crown Copyright 2022

www.webofpharma.com

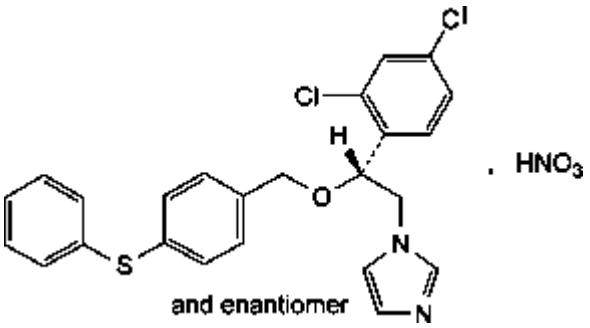
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fenticonazole Nitrate

General Notices

(Ph. Eur. monograph 1211)



$C_{24}H_{21}Cl_2N_3O_4S$ 518.4 *73151-29-8*

Action and use

Antifungal.

Ph Eur

DEFINITION

1-[(2*RS*)-2-(2,4-Dichlorophenyl)-2-[[4-(phenylsulfanyl)benzyl]oxy]ethyl]-1*H*-imidazole nitrate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in dimethylformamide and in methanol, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

First identification: C, D.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, B, D.

A. Melting point (2.2.14): 134 °C to 137 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20.0 mg in anhydrous ethanol R and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with anhydrous ethanol R.

Spectral range 230-350 nm.

Absorption maximum At 252 nm.

Shoulder At about 270 nm.

Absorption minimum At 236 nm.

Specific absorbance at the absorption maximum 260 to 280.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison fenticonazole nitrate CRS.

D. It gives the reaction of nitrates (2.3.1).

TESTS

Optical rotation (2.2.7)

-0.10° to + 0.10°.

Dissolve 0.10 g in methanol R and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 200.0 mL with the mobile phase.

Reference solution (b) Dilute 10.0 mL of reference solution (a) to 25.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (d) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dissolve the contents of a vial of fenticonazole impurity D CRS in 1.0 mL of this solution.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5-10 µm).

Mobile phase Mix 70 volumes of acetonitrile R1 and 30 volumes of a phosphate buffer solution prepared by dissolving 3.4 g of potassium dihydrogen phosphate R in 900 mL of water R, adjusting to pH 3.0 with phosphoric acid R and diluting to 1000 mL with water R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 10 µL.

Run time 5.5 times the retention time of fenticonazole.

System suitability:

— resolution: minimum 2.0 between the peaks due to impurity D and fenticonazole in the chromatogram obtained with reference solution (d);

— signal-to-noise ratio: minimum 5 for the principal peak in the chromatogram obtained with reference solution (c).

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard the peak due to the nitric ion (which corresponds to the dead volume of the column).

Toluene

Head-space gas chromatography (2.2.28): use the standard additions method.

Test solution Disperse 0.2 g of the substance to be examined in a 10 mL vial with 5 mL of water R.

Reference solution Mix 4 mg of toluene R with water R and dilute to 1000 mL with the same solvent. Place 5 mL of this solution in a 10 mL vial.

Column:

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R (film thickness 1.2 µm).

Carrier gas helium for chromatography R.

Split ratio 1:25.

www.webofpharma.com

https://thuocngocanh.com/

Column head pressure 40 kPa.

Static head-space conditions which may be used:

— *equilibration temperature*: 90 °C;

— *equilibration time*: 1 h.

Temperature:

— *column*: 80 °C;

— *injection port*: 180 °C;

— *detector*: 220 °C.

Detection Flame ionisation.

Injection 1 mL of the gaseous phase.

Limit:

— *toluene*: maximum 100 ppm.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.450 g in 50 mL of a mixture of equal volumes of *anhydrous acetic acid R* and *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 51.84 mg of $C_{24}H_{21}Cl_2N_3O_4S$.

STORAGE

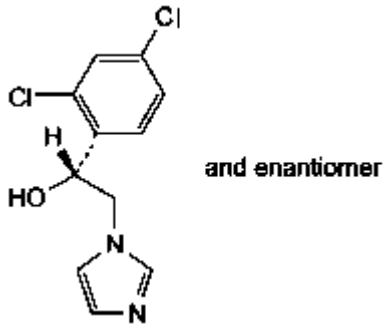
Protected from light.

IMPURITIES

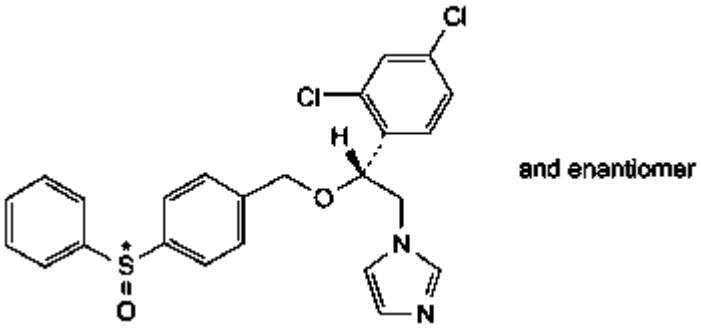
Specified impurities *A, B, C, D, E.*

www.webofpharma.com

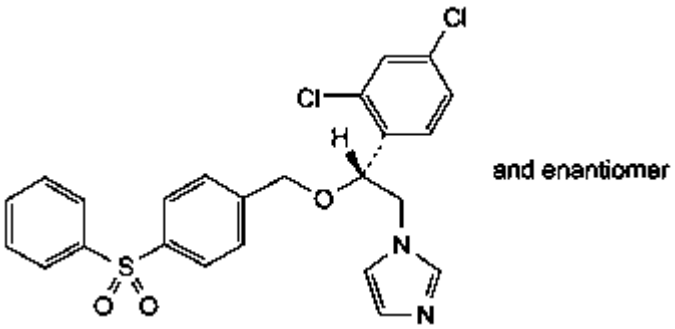
https://thuocngocanh.com/



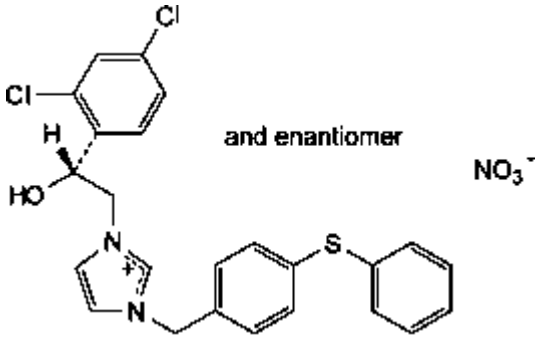
A. (*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol,



B. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[4-(benzenesulfinyl)benzyl]oxy]ethyl]-1*H*-imidazole,



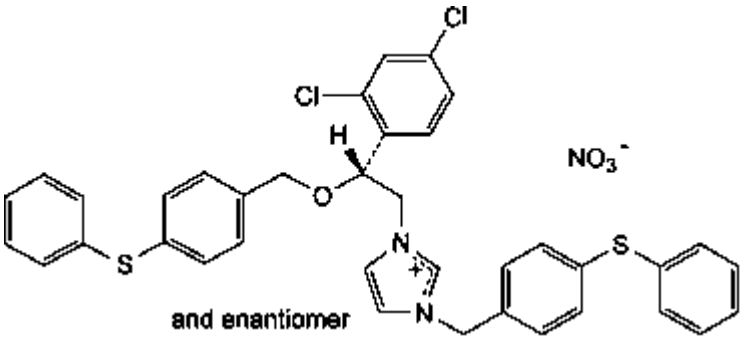
C. 1-[(2*RS*)-2-(2,4-dichlorophenyl)-2-[[4-(benzenesulfonyl)benzyl]oxy]ethyl]-1*H*-imidazole,



D. (*RS*)-1-[2-(2,4-dichlorophenyl)-2-hydroxyethyl]-3-[4-(phenylsulfanyl)benzyl]imidazolium nitrate,

www.webofpharma.com

https://thuocngocanh.com/



E. (*RS*)-1-[2-(2,4-dichlorophenyl)-2-[4-(phenylsulfanyl)benzyloxy]ethyl]-3-[4-(phenylsulfanyl)benzyl]imidazolium nitrate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferric Chloride Hexahydrate

General Notices

(Ph. Eur. monograph 1515)

$FeCl_3,6H_2O$ 270.3 *10025-77-1*

Preparation

Ferric Chloride Injection

Ph Eur

DEFINITION

Content

98.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

Crystalline mass or orange-yellow or brownish-yellow crystals, very hygroscopic.

Solubility

Very soluble in water and in ethanol (96 per cent), freely soluble in glycerol.

IDENTIFICATION

A. It gives reaction (a) of chlorides (*2.3.1*).

B. It gives reaction (c) of iron (*2.3.1*).

TESTS

Solution S

Dissolve 10 g in *distilled water R* and dilute to 100 mL with the same solvent.

Acidity

In a suitable polyethylene container, dissolve 3.0 g of *potassium fluoride R* in 15 mL of *water R*. Titrate with *0.1 M sodium hydroxide* using 0.1 mL of *phenolphthalein solution R* as indicator until a pink colour is obtained. Add 10 mL of solution S and allow to stand for 3 h. Filter

www.webofpharma.com

https://thuocngocanh.com/

and use 12.5 mL of the filtrate. Not more than 0.30 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Free chlorine

Heat 5 mL of solution S. The vapour does not turn *starch iodide paper R* blue.

Sulfates (*2.4.13*)

Maximum 100 ppm.

Heat 15 mL of solution S on a water-bath and add 5 mL of *strong sodium hydroxide solution R*. Allow to cool and filter. Neutralise the filtrate to *blue litmus paper R* using *hydrochloric acid R1* and evaporate to 15 mL.

Ferrous ions

Maximum 50 ppm.

To 10 mL of solution S, add 1 mL of *water R*, and 0.05 mL of *potassium ferricyanide solution R* followed by 4 mL of *phosphoric acid R*. After 10 min, any blue colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 10 mL of *water R* and 1 mL of a freshly prepared 0.250 g/L solution of *ferrous sulfate R*.

ASSAY

In a conical flask with a ground-glass stopper, dissolve 0.200 g in 20 mL of *water R*. Add 10 mL of *dilute hydrochloric acid R* and 2 g of *potassium iodide R*. Allow the stoppered flask to stand for 1 h protected from light. Titrate with *0.1 M sodium thiosulfate*, adding 5 mL of *starch solution R* towards the end of the titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 27.03 mg of $FeCl_3,6H_2O$.

STORAGE

In an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferric Chloride Injection

General Notices

Iron Chloride Injection

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Used in parenteral nutrition solutions.

DEFINITION

Ferric Chloride Injection is a sterile solution of Ferric Chloride Hexahydrate in a suitable liquid.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of ferric iron, Fe(III)

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Yields reaction C characteristic of *iron salts* and reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH, 1.7 to 2.4, Appendix V L.

5-Hydroxymethylfurfural

Injections prepared in Glucose Infusion comply with the following test.

Dilute a volume containing the equivalent of 1.0 g of glucose, $C_6H_{12}O_6$, to 250 mL with *water*. The *absorbance* of the resulting solution at the maximum at 284 nm is not more than 0.25, Appendix II B.

ASSAY

Carry out the method for *inductively coupled plasma-atomic emission spectrometry*, Appendix II G1, using a wavelength of 238.2 nm.

Dilute a quantity of the injection with sufficient 2% v/v *heavy metal-free nitric acid* to produce a solution containing 0.001% w/v of Fe.

www.webofpharma.com

https://thietbiuocngocanh.com/

Calculate the content of Fe in the injection from a calibration curve obtained from a series of reference solutions prepared in the following manner. Dilute 1 volume of *iron standard solution (0.1% Fe)* to 10 volumes; dilute separate 0, 5, 10 and 20 mL quantities of the resulting solution to 100 mL with 2% v/v *heavy metal-free nitric acid*.

LABELLING

The strength is stated as the equivalent amount of iron, Fe, in a suitable dose volume.

© Crown Copyright 2022

www.webofpharma.com

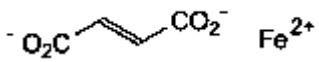
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Fumarate

General Notices

(Ph. Eur. monograph 0902)



$C_4H_2FeO_4$ 169.9 *141-01-5*

Action and use

Treatment of iron-deficiency anaemia.

Preparations

Ferrous Fumarate Capsules

Ferrous Fumarate Oral Suspension

Ferrous Fumarate Tablets

Ferrous Fumarate and Folic Acid Tablets

Ph Eur

DEFINITION

Iron(II) (*E*)-butenedioate.

Content

93.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Fine, reddish-orange or reddish-brown powder.

Solubility

Slightly soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution To 1.0 g add 25 mL of a mixture of equal volumes of *hydrochloric acid R* and *water R* and heat on a water-bath for 15 min. Cool and filter. Use the filtrate for identification test C. Wash the residue with 50 mL of a mixture of 1 volume of *dilute hydrochloric acid R* and 9 volumes of *water R* and discard the washings. Dry the residue at 100-105 °C. Dissolve 20 mg of the residue in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *fumaric acid CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *methylene chloride R*, *butanol R*, *heptane R* (12:16:32:44 *V/V/V/V*).

Application 5 µL.

Development In an unsaturated tank, over a path of 10 cm.

Drying At 105 °C for 15 min.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

B. Mix 0.5 g with 1 g of *resorcinol R*. To 0.5 g of the mixture in a crucible add 0.15 mL of *sulfuric acid R* and heat gently. A dark red semi-solid mass is formed. Add the mass, with care, to 100 mL of *water R*. An orange-yellow colour develops and the solution shows no fluorescence.

C. The filtrate obtained during preparation of the test solution in identification test A gives reaction (a) of iron (2.3.1).

TESTS

Sulfates (2.4.13)

Maximum 0.2 per cent.

Heat 0.15 g with 8 mL of *dilute hydrochloric acid R* and 20 mL of *distilled water R*. Cool in iced water, filter and dilute to 30 mL with *distilled water R*.

Elemental impurities

Any method that fulfils the requirements of general chapter 2.4.20. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Arsenic	1.5
Chromium	200

www.webofpharma.com

https://thuocngocanh.com/

Element	Maximum content (ppm)
Cobalt	20
Lead	3
Nickel	50
Vanadium	40

Ferric ion

Maximum 2.0 per cent.

In a flask with a ground-glass stopper, dissolve 3.0 g in a mixture of 10 mL of *hydrochloric acid R* and 100 mL of *water R* by heating rapidly to boiling. Boil for 15 s. Cool rapidly, add 3 g of *potassium iodide R*, stopper the flask and allow to stand protected from light for 15 min. Add 2 mL of *starch solution R* as indicator. Titrate the liberated iodine with *0.1 M sodium thiosulfate*. Carry out a blank test. The difference between the volumes used in the 2 titrations corresponds to the amount of iodine liberated by ferric ion.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 5.585 mg of ferric ion.

Zinc

Maximum 500 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dissolve 0.500 g in a mixture of 2.5 mL of *hydrochloric acid R* and 20 mL of *water R*, heating slightly if necessary. Allow to cool, filter if necessary and dilute to 25.0 mL with *water R*. Dilute 1.0 mL of the solution to 10.0 mL with *water R*.

Reference solutions Prepare the reference solutions using *zinc standard solution (10 ppm Zn) R* and diluting with a 1 per cent *V/V* solution of *hydrochloric acid R*.

Source Zinc hollow-cathode lamp.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve with slight heating 0.150 g in 7.5 mL of *dilute sulfuric acid R*. Cool and add 25 mL of *water R*. Add 0.1 mL of *ferroin R*. Titrate immediately with *0.1 M cerium sulfate* until the colour changes from orange to light bluish-green.

1 mL of *0.1 M cerium sulfate* is equivalent to 16.99 mg of $C_4H_2FeO_4$.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

In an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Fumarate and Folic Acid Capsules

General Notices

Action and use

Source of iron + Vitamin B component; used in treatment of iron-deficiency anaemia.

DEFINITION

Ferrous Fumarate and Folic Acid Capsules contain Ferrous Fumarate and Folic Acid Hydrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Carry out the tests avoiding exposure to actinic light.

Content of ferrous fumarate, $C_4H_2FeO_4$

90.0 to 105.0% of the stated amount.

Content of folic acid, $C_{19}H_{19}N_7O_6$

90.0 to 115.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the capsule contents containing the equivalent of 0.5 mg of folic acid with 1 mL of a mixture of 2 volumes of 13.5M *ammonia* and 9 volumes of *methanol*.

(2) 0.05% w/v of *folic acid BPCRS* in a mixture of 2 volumes of 13.5M *ammonia* and 9 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (366 nm)*.

MOBILE PHASE

20 volumes of 13.5 M *ammonia*, 20 volumes of *propan-1-ol* and 60 volumes of *ethanol (96%)*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) is similar in position, fluorescence and size to that in the chromatogram obtained with solution (2).

B. In the Assay for folic acid, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. Heat a quantity of the capsule contents containing 0.77 g of Ferrous Fumarate with 25 mL of a mixture of equal volumes of *hydrochloric acid* and *water* on a water bath for 15 minutes, cool and filter. Retain the residue for test D. The filtrate yields reaction A characteristic of *iron salts*, Appendix VI.

D. Wash the residue reserved in test C with a mixture of 1 volume of *2M hydrochloric acid* and 9 volumes of *water* and dry at 105°. Suspend 0.1 g of the residue in 2 mL of *sodium carbonate solution* and add *potassium permanganate solution* dropwise. The permanganate is decolourised and a brownish solution is produced.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

For folic acid

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 60 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with 0.1M *hydrochloric acid* if necessary, to produce a solution expected to contain 0.00004% w/v of folic acid.

(2) 0.00004% w/v of *folic acid BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed *with base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 300 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *formic acid*, 100 volumes of *methanol* and 900 volumes of *water*.

Mobile phase B 1 volume of *formic acid*, 100 volumes of *water* and 900 volumes of *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	100	0	isocratic
4-9.5	100→10	0→90	linear gradient
9.5-9.6	10→100	90→0	linear gradient
9.6-20	100	0	re-equilibration

DETERMINATION OF CONTENT

Calculate the total content of $C_{19}H_{19}N_7O_6$ in the medium from the chromatograms obtained and using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

LIMITS

The amount of folic acid released is not less than 75% (Q) of the stated amount.

For ferrous fumarate

PROCEDURE

After 60 minutes withdraw a sample of the medium and filter. Titrate 100 mL of the filtrate with 0.01M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator.

DETERMINATION OF CONTENT

Calculate the total content of $C_4H_2FeO_4$ in the medium taking each mL of 0.1M *ammonium cerium(IV) sulfate VS* to be equivalent to 16.99 mg of $C_4H_2FeO_4$.

The amount of ferrous fumarate released is not less than 75% (Q) of the stated amount.

Ferric iron

Shake a quantity of capsule contents containing 1.5 g of Ferrous Fumarate in a mixture of 100 mL of *water* and 10 mL of *hydrochloric acid* by heating rapidly to the boiling point. Boil for 15 seconds, cool rapidly, add 3 g of *potassium iodide*, stopper, allow to stand in the dark for 15 minutes and titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Repeat the operation without the substance being examined. The difference between the titrations is not more than 13.4 mL (5% ferric iron in Ferrous Fumarate).

Uniformity of Content

For folic acid

For capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid.

Complies with the requirements stated under Capsules using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 135 volumes of *methanol* and 800 volumes of a 0.57% w/v solution of *dipotassium hydrogen orthophosphate* (solvent A).

www.webofpharma.com

https://thuocngocanh.com/

(1) Place one capsule in 40 mL of solvent A, shake for a further 15 minutes, dilute to 50 mL with solvent A and filter (a 0.45-µm nylon filter is suitable).

(2) 0.0007% w/v of *folic acid BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 277 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

135 volumes of *methanol* and 800 volumes of a solution containing 0.938% w/v of *sodium perchlorate* and 0.075% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 7.2 with 0.1M *potassium hydroxide* and diluted to 1000 volumes with *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in each capsule using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

ASSAY

For ferrous fumarate

Weigh the contents of 20 capsules. Mix and powder if necessary. Mix a quantity of the capsule contents containing 0.3 g of Ferrous Fumarate with 7.5 mL of 1M *sulfuric acid* with gentle heating. Cool, add 25 mL of *water* and titrate immediately with *0.1M ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of *0.1M ammonium cerium(IV) sulfate VS* is equivalent to 16.99 mg of $C_4H_2FeO_4$.

For folic acid

For capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid

Use the average of the 10 individual results obtained in the test for Uniformity of content.

For capsules containing the equivalent of 2 mg or more and 2% w/w or more of folic acid

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 135 volumes of *methanol* and 800 volumes of a 0.57% w/v solution of *dipotassium hydrogen orthophosphate* (solvent A).

(1) Shake a quantity of the capsule contents containing the equivalent of 0.35 mg of folic acid with 40 mL of solvent A, mix for 5 minutes with the aid of ultrasound, shake for a further 15 minutes and dilute to 50 mL with solvent A and filter (a 0.45-µm nylon filter is suitable)

(2) 0.0007% w/v of *folic acid BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of Content may be used.

www.webofpharma.com

https://thietbiuocngocanh.com/

MOBILE PHASE

135 volumes of *methanol* and 800 volumes of a solution containing 0.938% w/v of *sodium perchlorate* and 0.075% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 7.2 with 0.1M *potassium hydroxide* and diluted to 1000 volumes with *water*.

When the chromatogram is recorded under the prescribed conditions, the retention time for folic acid is about 4.5 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in the capsules using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

STORAGE

Ferrous Fumarate and Folic Acid Capsules should be protected from light.

LABELLING

For *ferrous fumarate* the quantity of the active ingredient is stated both as the amount of ferrous fumarate and in terms of the equivalent amount of ferrous iron.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Fumarate and Folic Acid Tablets

General Notices

Action and use

Source of iron + Vitamin B component; used in treatment of iron-deficiency anaemia.

DEFINITION

Ferrous Fumarate and Folic Acid Tablets contain Ferrous Fumarate and Folic Acid Hydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Carry out the tests avoiding exposure to actinic light.

Content of ferrous fumarate, $C_4H_2FeO_4$

90.0 to 105.0% of the stated amount.

Content of folic acid, $C_{19}H_{19}N_7O_6$

90.0 to 115.0% of the stated amount.

IDENTIFICATION

A. In the Assay for folic acid, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

B. Heat a quantity of the powdered tablets containing 0.77 g of Ferrous Fumarate with 25 mL of a mixture of equal volumes of *hydrochloric acid* and *water* on a water bath for 15 minutes, cool and filter. Retain the residue for test C. The filtrate yields reaction A characteristic of *iron salts*, Appendix VI.

C. Wash the residue reserved in test B with a mixture of 1 volume of *2M hydrochloric acid* and 9 volumes of *water* and dry at 105°. Suspend 0.1 g of the residue in 2 mL of *sodium carbonate solution* and add *potassium permanganate solution* dropwise. The permanganate is decolourised and a brownish solution is produced.

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

www.webofpharma.com

https://thuocngocanh.com/

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

For folic acid

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 60 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with 0.1M *hydrochloric acid* if necessary, expected to contain 0.00004% w/v of folic acid.

(2) Disperse 10 mg of *folic acid BPCRS* in 75 mL of *methanol* and mix with the aid ultrasound for 15 minutes. Add 125 mL of 0.1M *hydrochloric acid*, mix with the aid of ultrasound for a further 15 minutes and dilute to 250 mL with 0.1M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 100 volumes with 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed *with* *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 300 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *formic acid*, 100 volumes of *methanol* and 900 volumes of *water*.

Mobile phase B 1 volume of *formic acid*, 100 volumes of *water* and 900 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	100	0	isocratic
4-9.5	100→10	0→90	linear gradient
9.5-9.6	10→100	90→0	linear gradient
9.6-20	100	0	re-equilibration

DETERMINATION OF CONTENT

Calculate the total content of $C_{19}H_{19}N_7O_6$ in the medium from the chromatograms obtained and using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

LIMITS

The amount of folic acid released is not less than 75% (Q) of the stated amount.

www.webofpharma.com

https://thuocngocanh.com/

For ferrous fumarate

PROCEDURE

After 60 minutes withdraw a sample of the medium and filter. Titrate 100 mL of the filtrate with 0.01M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator.

DETERMINATION OF CONTENT

Calculate the total content of $C_4H_2FeO_4$ in the medium taking each mL of 0.1M *ammonium cerium(IV) sulfate VS* to be equivalent to 16.99 mg of $C_4H_2FeO_4$.

The amount of ferrous fumarate released is not less than 75% (Q) of the stated amount.

Ferric iron

Dissolve a quantity of the powder prepared for the Assay for ferrous fumarate containing 1.5 g of Ferrous Fumarate in a mixture of 100 mL of *water* and 10 mL of *hydrochloric acid* by heating rapidly to the boiling point. Boil for 15 seconds, cool rapidly, add 3 g of *potassium iodide*, stopper, allow to stand in the dark for 15 minutes and titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Repeat the operation without the substance being examined. The difference between the titrations is not more than 13.4 mL (5% ferric iron in Ferrous Fumarate).

Uniformity of Content

For folic acid

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid.

Complies with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 135 volumes of *methanol* and 800 volumes of a 0.57% w/v solution of *dipotassium hydrogen orthophosphate* (solvent A).

(1) Place one tablet in 40 mL of solvent A, shake for a further 15 minutes, dilute to 50 mL with solvent A and filter (a 0.45-µm nylon filter is suitable).
(2) 0.0007% w/v of *folic acid BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 277 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

135 volumes of *methanol* and 800 volumes of a solution containing 0.938% w/v of *sodium perchlorate* and 0.075% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 7.2 with 0.1M *potassium hydroxide* and diluted to 1000 volumes with *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in each tablet using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

ASSAY

Weigh and powder 20 tablets.

For ferrous fumarate

Disperse a quantity of the powder containing 0.3 g of Ferrous Fumarate in 7.5 mL of 1M *sulfuric acid* with gentle heating. Cool, add 25 mL of *water* and titrate immediately with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium (IV) sulfate VS* is equivalent to 16.99 mg of $C_4H_2FeO_4$.

For folic acid

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid

Use the average of the individual results obtained in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of folic acid

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 135 volumes of *methanol* and 800 volumes of a 0.57% w/v solution of *dipotassium hydrogen orthophosphate* (solvent A).

(1) Mix a quantity of the powdered tablets containing the equivalent of 0.35 mg of folic acid in 40 mL of solvent A, mix for 5 minutes with the aid of ultrasound, shake for a further 15 minutes and dilute to 50 mL with solvent A and filter (a 0.45-µm nylon filter is suitable).
(2) 0.0007% w/v of *folic acid BPCRS* solvent A.

CHROMATOGRAPHIC CONDITIONS

Chromatographic conditions described under Uniformity of Content may be used.

MOBILE PHASE

135 volumes of *methanol* and 800 volumes of a solution containing 0.938% w/v of *sodium perchlorate* and 0.075% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 7.2 with 0.1M *potassium hydroxide* and diluted to 1000 volumes with *water*.

When the chromatogram is recorded under the prescribed conditions, the retention time for folic acid is about 4.5 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in the tablets using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

STORAGE

Ferrous Fumarate and Folic Acid Tablets should be protected from light.

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

For *ferrous fumarate* the quantity of the active ingredient is stated both as the amount of ferrous fumarate and in terms of the equivalent amount of ferrous iron.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Fumarate Capsules

General Notices

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Ferrous Fumarate Capsules contain Ferrous Fumarate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of ferrous iron, Fe(II)

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Heat 1 g of the contents of the capsules with 25 mL of a mixture of equal volumes of *hydrochloric acid* and *water* on a water bath for 15 minutes, cool and filter. Retain the residue for test B. The filtrate yields reaction A characteristic of *iron salts*, Appendix VI.

B. Wash the residue reserved in test A with a mixture of 1 volume of 2M *hydrochloric acid* and 9 volumes of *water* and dry at 105°. Suspend 0.1 g of the residue in 2 mL of *dilute sodium carbonate solution* and add *dilute potassium permanganate solution* drop wise. The permanganate is decolourised and a brownish solution is produced.

C. Mix a quantity of the contents of the capsules containing 0.5 g of Ferrous Fumarate with 1 g of *resorcinol*. To 0.5 g of the mixture in a crucible add 0.15 mL of *sulfuric acid* and heat gently; a deep red, semi-solid mass is produced. Add the mass to a large volume of *water*; an orange–yellow solution is produced which exhibits no fluorescence.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a sample of the medium and filter. Titrate 100 mL of the filtrate with *0.01M ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of Fe(II) in the medium taking each mL of *0.01M ammonium cerium(IV) sulfate VS* to be equivalent to 0.5585 mg of Fe(II).

Ferric iron

In a flask with a ground-glass stopper dissolve a quantity of the mixed capsule contents prepared for the Assay containing 1.5 g of Ferrous Fumarate in a mixture of 10 mL of *hydrochloric acid* and 100 mL of *water* by heating rapidly to boiling. Boil for 15 seconds. Cool rapidly, add 3 g of *potassium iodide*, stopper the flask and allow to stand protected from light for 15 minutes. Add 2 mL of *starch solution* as indicator. Titrate the liberated iodine with 0.1M *sodium thiosulfate VS*. Carry out a blank test. The difference between the volumes used in the two titrations corresponds to the amount of iodine liberated by ferric iron. The difference between the titrations is not more than 13.4 mL (5%).

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Dissolve a quantity of the mixed capsule contents containing 0.3 g of Ferrous Fumarate in 7.5 mL of 1M *sulfuric acid* with gentle heating. Cool, add 25 mL of *water* and titrate immediately with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 5.585 mg of Fe(II).

LABELLING

The quantity of the active ingredient is stated both as the amount of ferrous fumarate and in terms of the equivalent amount of ferrous iron.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Fumarate Oral Suspension

General Notices

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Ferrous Fumarate Oral Suspension is a suspension of Ferrous Fumarate in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of ferrous iron, Fe(II)

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Mix a volume of the oral suspension containing about 0.6 g of Ferrous Fumarate with 20 mL of *water*, centrifuge and discard the supernatant liquid. Repeat with a further 20 mL of *water*. Add 15 mL of *3M hydrochloric acid* to the residue, dissolve with minimum warming, cool and extract with two 50-mL quantities of *ether*. Wash the combined ether extracts with two 20-mL quantities of *water*, shake with *anhydrous sodium sulfate*, filter and evaporate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fumaric acid *(RS 163)*.

B. Mix a volume of the oral suspension containing about 0.3 g of Ferrous Fumarate in 10 mL of *water*, centrifuge and discard the supernatant liquid. To 0.2 g of the residue add 10 mL of a mixture of equal volumes of *hydrochloric acid* and *water*, dissolve with minimum warming, cool and filter. The filtrate yields reaction A characteristic of *iron salts*, Appendix VI.

TESTS

Ferric iron

Disperse a quantity of the oral suspension containing 0.28 g of Ferrous Fumarate in 20 mL of *water*, centrifuge and decant the supernatant liquid into a 500-mL graduated flask. Dissolve the residue in 20 mL of 1M *sulfuric acid* with minimum warming, cool and transfer the resulting solution to the same graduated flask, dilute to 500 mL with *water* and filter. To 5 mL of the filtrate in a *Nessler cylinder* add 40 mL of *water* and 5 mL of a 10% w/v solution of *ammonium thiocyanate* and mix. Any red colour produced is not more intense than that obtained by treating in the same manner a mixture of 42 mL of *water*, 0.2 mL of 1M *sulfuric acid* and 3 mL of a 0.0173% w/v solution of *ammonium iron(III) sulfate* in 0.01M *hydrochloric acid* [6.0%, with respect to the content of Fe(II)].

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Mix a quantity of the oral suspension containing 0.28 g of Ferrous Fumarate with 10 mL of *water* and 25 mL of *nitric acid*, carefully warm until the vigorous reaction subsides, add a further 25 mL of *nitric acid*, evaporate to about 10 mL and allow to cool. Carefully add 10 mL of *sulfuric acid* to the cooled solution, evaporate until white fumes are evolved, cool, add 10 mL of *nitric acid* and again evaporate until white fumes are evolved. Repeat the evaporation with 10 mL quantities of *nitric acid* until all of the organic matter has been destroyed. To the resulting solution add 10 mL of *water* and 0.5 g of *ammonium oxalate*, evaporate until white fumes are evolved, add 50 mL of *water*, boil until a clear solution is obtained, cool, dilute to 100 mL with *water* and add *dilute potassium permanganate solution*, drop wise, until a faint pink colour persists for 10 seconds. Add 10 mL of *hydrochloric acid* and 3 g of *potassium iodide*, allow to stand for 15 minutes protected from light, add 10 mL of *chloroform* and titrate the liberated iodine with 0.1M *sodium thiosulfate VS*, with vigorous shaking, until the chloroform layer becomes colourless. Repeat the procedure without the preparation being examined. The difference between the titrations represents the amount of sodium thiosulfate required. Each mL of 0.1M *sodium thiosulfate VS* is equivalent to 5.585 mg of Fe(II).

STORAGE

Ferrous Fumarate Oral Suspension should be protected from light.

LABELLING

The quantity of the active ingredient is stated both as the amount of ferrous fumarate and in terms of the equivalent amount of ferrous iron.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Fumarate Tablets

General Notices

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Ferrous Fumarate Tablets contain Ferrous Fumarate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ferrous iron, Fe(II)

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Heat 1 g of the powdered tablets with 25 mL of a mixture of equal volumes of *hydrochloric acid* and *water* on a water bath for 15 minutes, cool and filter. Retain the residue for test B. The filtrate yields reaction A characteristic of *iron salts*, Appendix VI.

B. Wash the residue reserved in Test A with a mixture of 1 volume of *2M hydrochloric acid* and 9 volumes of *water* and dry at 105°. Suspend 0.1 g of the residue in 2 mL of *dilute sodium carbonate solution* and add *dilute potassium permanganate solution* drop wise. The permanganate is decolourised and a brownish solution is produced.

C. Mix a quantity of the powdered tablets containing 0.5 g of Ferrous Fumarate with 1 g of *resorcinol*. To 0.5 g of the mixture in a crucible add 0.15 mL of *sulfuric acid* and heat gently; a deep red, semi-solid mass is produced. Add the mass to a large volume of *water*; an orange–yellow solution is produced which exhibits no fluorescence.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a sample of 100 mL of the medium and filter. Titrate the filtrate with 0.01M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of Fe(II) in the medium taking each mL of 0.01M *ammonium cerium(IV) sulfate VS* to be equivalent to 0.5585 mg of Fe(II).

Ferric iron

In a flask with a ground-glass stopper dissolve a quantity of the powder prepared for the Assay containing 1.5 g of Ferrous Fumarate in a mixture of 10 mL of *hydrochloric acid* and 100 mL of *water* by heating rapidly to boiling. Boil for 15 seconds. Cool rapidly, add 3 g of *potassium iodide*, stopper the flask and allow to stand protected from light for 15 minutes. Add 2 mL of *starch solution* as indicator. Titrate the liberated iodine with 0.1M *sodium thiosulfate VS*. Carry out a blank test. The difference between the volumes used in the two titrations corresponds to the amount of iodine liberated by ferric ion. The difference between the titrations is not more than 13.4 mL (5%).

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.3 g of Ferrous Fumarate in 7.5 mL of 1M *sulfuric acid* with gentle heating. Cool, add 25 mL of *water* and titrate immediately with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 5.585 mg of Fe(II).

LABELLING

The quantity of the active ingredient is stated both as the amount of ferrous fumarate and in terms of the equivalent amount of ferrous iron.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

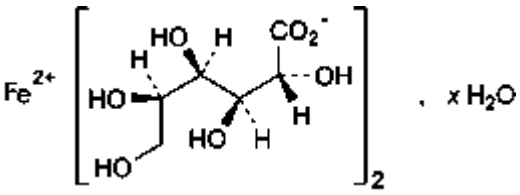
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Gluconate Hydrate

General Notices

Ferrous Gluconate

(Ph. Eur. monograph 0493)



$C_{12}H_{22}FeO_{14},xH_2O$ 446.1 (anhydrous substance)

Action and use

Used in prevention and treatment of iron deficiency.

Preparation

Ferrous Gluconate Tablets

Ph Eur

DEFINITION

Iron(II) bis[(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate] (iron(II) di(D-gluconate)) hydrate.

Content

11.8 per cent to 12.5 per cent of iron(II) (dried substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

Greenish-yellow or grey powder or granules.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely but slowly soluble in water giving a greenish-brown solution, more readily soluble in hot water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 2 mL of *water R*, heating if necessary in a water-bath at 60 °C.

Reference solution Dissolve 20 mg of *ferrous gluconate CRS* in 2 mL of *water R*, heating if necessary in a water-bath at 60 °C.

Plate *TLC silica gel plate R* (5-40 µm) [or *TLC silica gel plate R* (2-10 µm)].

Mobile phase *concentrated ammonia R*, *ethyl acetate R*, *water R*, *ethanol (96 per cent) R* (10:10:30:50 *V/V/V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying At 105 °C for 20 min; allow to cool.

Detection Spray with a solution containing 10 g/L of *cerium sulfate R* and 25 g/L of *ammonium molybdate R* in *dilute sulfuric acid R* and heat at 105 °C for about 10 min.

Results After 5 min, the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. 1 mL of solution S (see Tests) gives reaction (a) of iron (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and heated to about 60 °C, allow to cool and dilute to 20 mL with *carbon dioxide-free water R* prepared from *distilled water R*.

Appearance of solution

The solution is clear (2.2.1).

Dilute 2 mL of solution S to 10 mL with *water R*. Examine the solution against the light.

pH (2.2.3)

4.0 to 5.5 for solution S, measured 3-4 h after preparation.

Sucrose and reducing sugars

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.5 g in 10 mL of warm *water R* and add 1 mL of *dilute ammonia R1*. Pass *hydrogen sulfide R* through the solution and allow to stand for 30 min. Filter and wash the precipitate with 2 quantities, each of 5 mL, of *water R*. Acidify the combined filtrate and washings to *blue litmus paper R* with *dilute hydrochloric acid R* and add 2 mL in excess. Boil until the vapour no longer darkens *lead acetate paper R* and continue boiling, if necessary, until the volume is reduced to about 10 mL. Cool, add 15 mL of *sodium carbonate solution R*, allow to stand for 5 min and filter. Dilute the filtrate to 100 mL with *water R*. To 5 mL of this solution add 2 mL of *cupri-tartaric solution R* and boil for 1 min. Allow to stand for 1 min. No red precipitate is formed.

Chlorides (*2.4.4*)

Maximum 0.06 per cent.

Dilute 0.8 mL of solution S to 15 mL with *water R*.

Oxalates

Dissolve 5.0 g in a mixture of 10 mL of *dilute sulfuric acid R* and 40 mL of *water R*. Shake the solution with 50 mL of *ether R* for 5 min. Separate the aqueous layer and shake it with 20 mL of *ether R* for 5 min. Combine the ether layers, evaporate to dryness and dissolve the residue in 15 mL of *water R*. Filter, boil the filtrate until the volume is reduced to 5 mL and add 1 mL of *dilute acetic acid R* and 1.5 mL of *calcium chloride solution R*. Allow to stand for 30 min. No precipitate is formed.

Sulfates (*2.4.13*)

Maximum 500 ppm.

To 3.0 mL of solution S add 3 mL of *acetic acid R* and dilute to 15 mL with *distilled water R*. Examine the solutions against the light.

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20*. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Arsenic	2
Cobalt	25
Nickel	50
Vanadium	50

Ferric ions

Maximum 1.0 per cent.

In a ground-glass-stoppered flask, dissolve 5.00 g in a mixture of 10 mL of *hydrochloric acid R* and 100 mL of *carbon dioxide-free water R*. Add 3 g of *potassium iodide R*, close the flask and allow to stand protected from light for 5 min. Titrate with *0.1 M sodium thiosulfate*, using 0.5 mL of *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration. Not more than 9.0 mL of *0.1 M sodium thiosulfate* is used.

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

5.0 per cent to 10.5 per cent, determined on 0.500 g by drying in an oven at 105 °C for 5 h.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

ASSAY

Dissolve 0.5 g of *sodium hydrogen carbonate R* in a mixture of 30 mL of *dilute sulfuric acid R* and 70 mL of *water R*. When the effervescence stops, dissolve 1.00 g of the substance to be examined with gentle shaking. Using 0.1 mL of *ferroin R* as indicator, titrate with *0.1 M ammonium and cerium nitrate* until the red colour disappears.

1 mL of *0.1 M ammonium and cerium nitrate* is equivalent to 5.585 mg of iron(II).

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Gluconate Tablets

General Notices

Action and use

Used in prevention and treatment of iron deficiency.

DEFINITION

Ferrous Gluconate Tablets contain Ferrous Gluconate Hydrate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ferrous iron, Fe(II)

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Ferrous Gluconate Hydrate with 10 mL of 2M *hydrochloric acid*, filter and add to the filtrate 1 mL of *barium chloride solution*. An opalescence may be produced but no precipitate is produced.

B. The powdered tablets yield reaction A characteristic of *iron salts*, Appendix VI.

TESTS

Ferric iron

Dissolve a quantity of the powder prepared for the Assay containing 5 g of Ferrous Gluconate Hydrate as completely as possible, without heating, in a mixture of 100 mL of freshly boiled and cooled *water* and 10 mL of *hydrochloric acid*; add 3 g of *potassium iodide*. Close the vessel, allow to stand in the dark for 5 minutes and titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Repeat the operation without the powder. The difference between the titrations represents the amount of iodine liberated by the ferric iron. Not more than 11.2 mL of 0.1M *sodium thiosulfate VS* is required.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 1 g of Ferrous Gluconate Hydrate as completely as possible in a mixture of 30 mL of *water* and 20 mL of 1M *sulfuric acid* and titrate with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 5.585 mg of Fe(II).

LABELLING

The quantity of active ingredient is stated both as the amount of ferrous gluconate and in terms of the equivalent amount of ferrous iron.

www.webofpharma.com

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Sulfate Heptahydrate

General Notices

Ferrous Sulphate Heptahydrate

(Ph. Eur. monograph 0083)

$FeSO_4,7H_2O$ 278.0 *7782-63-0*

Action and use

Treatment of iron-deficiency anaemia.

Preparation

Paediatric Ferrous Sulfate Oral Solution

Ph Eur

DEFINITION

Content

98.0 per cent to 105.0 per cent.

CHARACTERS

Appearance

Light green, crystalline powder or bluish-green crystals, efflorescent in air.

Solubility

Freely soluble in water, very soluble in boiling water, practically insoluble in ethanol (96 per cent).

Ferrous sulfate heptahydrate is oxidised in moist air, becoming brown.

IDENTIFICATION

A. It gives the reactions of sulfates (*2.3.1*).

B. It gives reaction (a) of iron (*2.3.1*).

C. It complies with the limits of the assay.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 4.0 g in a 5 per cent *V/V* solution of *lead-free nitric acid R* and dilute to 100.0 mL with the same solution.

pH (*2.2.3*)

3.0 to 4.0.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dilute 5 mL of solution S to 10 mL with *water R* and add 5 mL of *dilute nitric acid R*. Prepare the standard with a mixture of 2 mL of *water R*, 5 mL of *dilute nitric acid R* and 8 mL of *chloride standard solution (5 ppm Cl) R*. Use 0.15 mL of *silver nitrate solution R2* in this test.

Elemental impurities

Any method that fulfils the requirements of general chapter *2.4.20*. *Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Chromium	50
Cobalt	25
Copper	50
Nickel	50

Ferric ions

Maximum 0.3 per cent.

In a ground-glass-stoppered flask, dissolve 5.00 g in a mixture of 10 mL of *hydrochloric acid R* and 100 mL of *carbon dioxide-free water R*. Add 3 g of *potassium iodide R*, close the flask and allow to stand in the dark for 5 min. Titrate the liberated iodine with *0.1 M sodium thiosulfate*, using 0.5 mL of *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank test in the same conditions. Not more than 2.7 mL of *0.1 M sodium thiosulfate* is used, taking into account the blank titration.

Manganese

Maximum 0.1 per cent.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Dilute 1.0 mL of solution S to 20.0 mL with a 5 per cent *V/V* solution of *lead-free nitric acid R*.

Reference solutions Prepare the reference solutions using *manganese standard solution (1000 ppm Mn) R*, diluting with a 5 per cent *V/V* solution of *lead-free nitric acid R*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Source Manganese hollow-cathode lamp using a transmission band preferably of 1 nm.

Wavelength 279.5 nm.

Atomisation device Air-acetylene flame.

Zinc

Maximum 50 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Solution S.

Reference solutions Prepare the reference solutions using *zinc standard solution (100 ppm Zn) R*, diluting with a 5 per cent *V/V* solution of *lead-free nitric acid R*.

Source Zinc hollow-cathode lamp using a transmission band preferably of 1 nm.

Wavelength 213.9 nm.

Atomisation device Air-acetylene flame.

ASSAY

Dissolve 2.5 g of *sodium hydrogen carbonate R* in a mixture of 150 mL of *water R* and 10 mL of *sulfuric acid R*. When the effervescence ceases add to the solution 0.500 g of the substance to be examined and dissolve with gentle swirling. Add 0.1 mL of *ferroin R* and titrate with *0.1 M ammonium and cerium nitrate* until the red colour disappears.

1 mL of *0.1 M ammonium and cerium nitrate* is equivalent to 27.80 mg of $FeSO_4,7H_2O$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Sulfate Prolonged-release Tablets

General Notices

Ferrous Sulphate Prolonged-release Tablets

Prolonged-release Ferrous Sulfate Tablets

Ferrous Sulfate Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Ferrous Sulfate Prolonged-release Tablets contain Dried Ferrous Sulfate. They are formulated so that the medicament is released over a period of several hours. They are coated.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of ferrous sulfate. The dissolution profile should reflect the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ferrous iron, Fe(II)

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The powdered tablets yield reaction A characteristic of *iron salts*, Appendix VI.

B. Extract a quantity of the powdered tablets containing 0.15 g of Dried Ferrous Sulfate with 10 mL of *2M hydrochloric acid* and filter. The filtrate yields reaction A characteristic of *sulfates*, Appendix VI.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.5 g of Dried Ferrous Sulfate as completely as possible in a mixture of 30 mL of *water* and 20 mL of 1M *sulfuric acid* and titrate with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 5.585 mg of Fe(II).

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The quantity of active ingredient is stated both as the amount of dried ferrous sulfate and in terms of the equivalent amount of ferrous iron.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ferrous Sulfate Tablets

General Notices

Ferrous Sulphate Tablets

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Ferrous Sulfate Tablets contain Dried Ferrous Sulfate. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ferrous iron, Fe(II)

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The powdered tablets yield reaction A characteristic of *iron salts*, Appendix VI.

B. Extract the powdered tablets with 2M *hydrochloric acid* and filter. The filtrate yields reaction A characteristic of *sulfates*, Appendix VI.

ASSAY

Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.5 g of Dried Ferrous Sulfate as completely as possible in a mixture of 30 mL of *water* and 20 mL of 1M *sulfuric acid* and titrate with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 5.585 mg of Fe(II).

LABELLING

The quantity of active ingredient is stated both as the amount of dried ferrous sulfate and in terms of the equivalent amount of ferrous iron.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

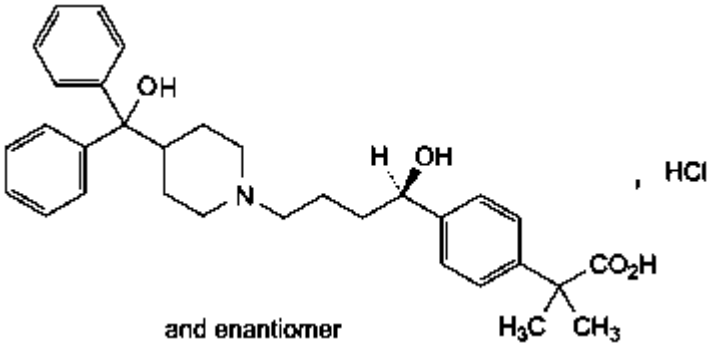
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fexofenadine Hydrochloride

General Notices

(Ph. Eur. monograph 2280)



$C_{32}H_{40}ClNO_4$ 538.1 *153439-40-8*

Action and use

Histamine H_1 receptor antagonist; antihistamine.

Preparation

Fexofenadine Tablets

Ph Eur

DEFINITION

2-[4-[(1*RS*)-1-Hydroxy-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butyl]phenyl]-2-methylpropanoic acid hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, freely soluble in methanol, very slightly soluble in acetone.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *fexofenadine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Dissolve 30 mg of the substance to be examined in a mixture of equal volumes of *methanol R* and *water R*; sonicate if necessary and dilute to 2 mL with the same mixture of solvents. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Impurity B

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *fexofenadine impurity B CRS* in the test solution and dilute to 2.0 mL with the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel BC for chiral chromatography R* (5 µm).

Mobile phase Mix 20 volumes of *acetonitrile for chromatography R* and 80 volumes of a buffer solution prepared as follows: to 1.15 mL of *glacial acetic acid R* add *water for chromatography R*, adjust to pH 4.0 ± 0.1 with *dilute ammonia R1* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 1.2 times the retention time of fexofenadine.

Relative retention With reference to fexofenadine (retention time = about 20 min): impurity B = about 0.7.

System suitability Reference solution (a):

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *resolution*: minimum 3.0 between the peaks due to fexofenadine and impurity B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 1.3;

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution Dissolve 6.64 g of *sodium dihydrogen phosphate monohydrate R* and 0.84 g of *sodium perchlorate R* in *water for chromatography R*, adjust to pH 2.0 ± 0.1 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Solvent mixture Mix equal volumes of *acetonitrile for chromatography R* and the buffer solution.

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 25.0 mL of the solvent mixture.

Test solution (b) Dilute 3.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *fexofenadine hydrochloride CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 3.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 1 mg each of *fexofenadine impurity A CRS* and *fexofenadine impurity C CRS* in 20 mL of reference solution (a) and dilute to 200.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 350 volumes of *acetonitrile for chromatography R* and 650 volumes of the buffer solution; add 3 volumes of *triethylamine R* and mix.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (b) and (c).

Relative retention With reference to fexofenadine (retention time = about 9 min): impurity A = about 1.7; impurity D = about 2.3; impurity C = about 3.2.

www.webofpharma.com

https://thuocngocanh.com/

Run time 6 times the retention time of fexofenadine for test solution (a) and reference solution (c), twice the retention time of fexofenadine for reference solution (b).

System suitability Reference solution (c):

— *resolution*: minimum 10 between the peaks due to fexofenadine and impurity A.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.4;

— *impurities A, C, D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.32)

Maximum 0.5 per cent.

Dissolve 1.000 g in *anhydrous methanol R* and dilute to 5.0 mL with the same solvent. Use 1.0 mL of this solution.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (a).

Run time Twice the retention time of fexofenadine.

Calculate the percentage content of fexofenadine hydrochloride from the declared content of *fexofenadine hydrochloride CRS*.

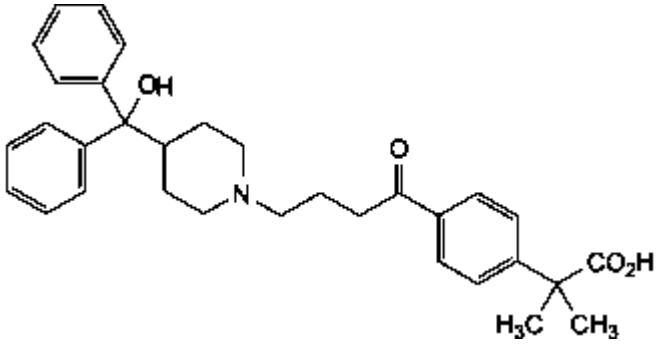
IMPURITIES

Specified impurities *A, B, C, D.*

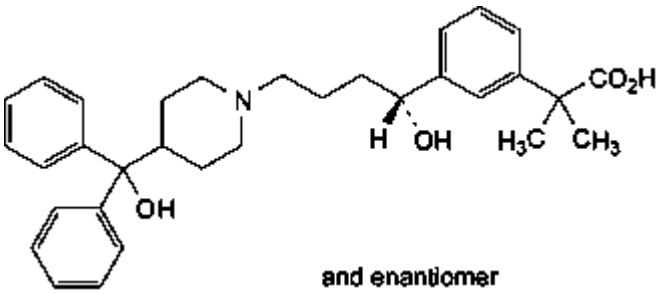
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F, G.*

www.webofpharma.com

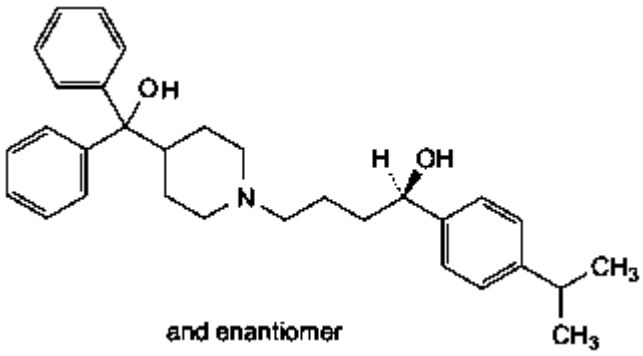
https://thuocngocanh.com/



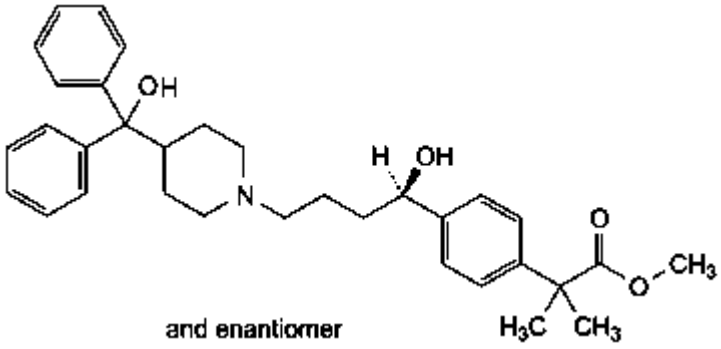
A. 2-[4-[4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butanoyl]phenyl]-2-methylpropanoic acid,



B. 2-[3-[(1*RS*)-1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butyl]phenyl]-2-methylpropanoic acid,



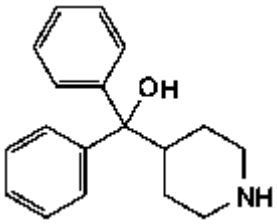
C. (1*RS*)-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]-1-[4-(1-methylethyl)phenyl]butan-1-ol,



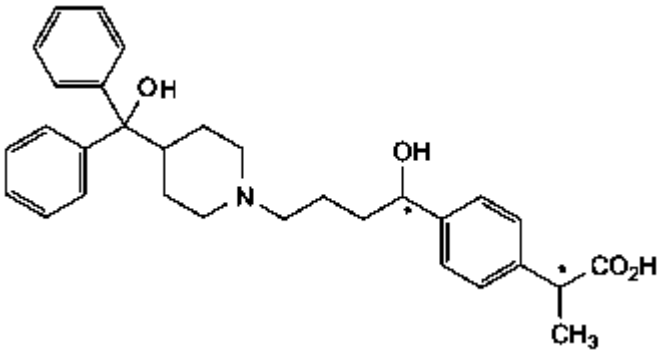
D. methyl 2-[4-[(1*RS*)-1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butyl]phenyl]-2-methylpropanoate,

www.webofpharma.com

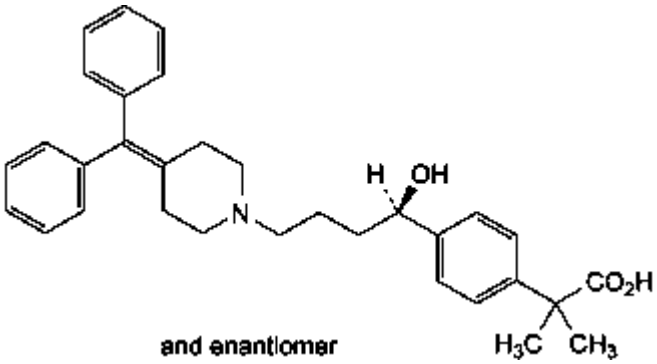
https://thuocngocanh.com/



E. diphenyl(piperidin-4-yl)methanol,



F. 2-[4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butyl]phenyl]propanoic acid,



G. 2-[4-[(1*RS*)-4-[4-(diphenylmethylidene)piperidin-1-yl]-1-hydroxybutyl]phenyl]-2-methylpropanoic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fexofenadine Tablets

General Notices

Action and use

Histamine H_1 receptor antagonist; antihistamine.

DEFINITION

Fexofenadine Tablets contain Fexofenadine Hydrochloride. They may be coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

The manufacturing process of Fexofenadine Hydrochloride, used in the formulation of Fexofenadine Tablets, is validated to ensure that the content of the enantiomer impurity B is not more than 0.1%.

Content of fexofenadine hydrochloride, $C_{32}H_{39}NO_4,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 30 mg of Fexofenadine Hydrochloride with 10 mL of *methanol* for 5 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of fexofenadine hydrochloride (*RS 459*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.001M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with 0.001M *hydrochloric acid* if necessary, to produce a solution expected to contain 0.003% w/v of Fexofenadine Hydrochloride.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.003% w/v of *fexofenadine hydrochloride BPCRS* in 0.001M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of fexofenadine hydrochloride, $C_{32}H_{39}NO_4$,HCl, in the medium from the chromatograms obtained and using the declared content of $C_{32}H_{39}NO_4$,HCl in *fexofenadine hydrochloride BPCRS*.

LIMITS

The amount of fexofenadine hydrochloride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A.

SOLVENT A

Equal volumes of *acetonitrile* and a buffer solution containing 0.05M *sodium dihydrogen orthophosphate monohydrate* and 0.006M *sodium perchlorate*. The pH of the buffer solution is adjusted to 2.0 with *orthophosphoric acid* before the addition of acetonitrile.

(1) Shake a quantity of powdered tablets containing 25 mg of Fexofenadine Hydrochloride with 25 mL of solvent A and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A and further dilute 1 volume of the resulting solution to 5 volumes with solvent A.
(3) 0.1% w/v of *fexofenadine impurity standard BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Zorbax SB Phenyl is suitable).
(b) Use isocratic elution using the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

350 volumes of *acetonitrile* and 650 volumes of a buffer solution containing 0.05M *sodium dihydrogen orthophosphate monohydrate* and 0.006M *sodium perchlorate* the pH of which is adjusted to 2.0 with *orthophosphoric acid*. To the resulting solution add 3 volumes of *triethylamine* and mix.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the principal peaks due to Fexofenadine and impurity A is at least 10.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

multiply the peak area of any peak corresponding to impurity A by 1.4;

the area of any *secondary peak* corresponding to impurity A is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any *secondary peak* corresponding to impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 50 mg of Fexofenadine Hydrochloride with 50 mL of solvent A and filter.

(2) 0.1% w/v of *fexofenadine hydrochloride BPCRS* in solvent A.

(3) 0.1% w/v of *fexofenadine impurity standard BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the principal peaks due to Fexofenadine and impurity A is at least 10.

DETERMINATION OF CONTENT

Calculate the content of $C_{32}H_{39}NO_4$,HCl in the tablets using the declared content of $C_{32}H_{39}NO_4$,HCl in *fexofenadine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and C listed under Fexofenadine Hydrochloride.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

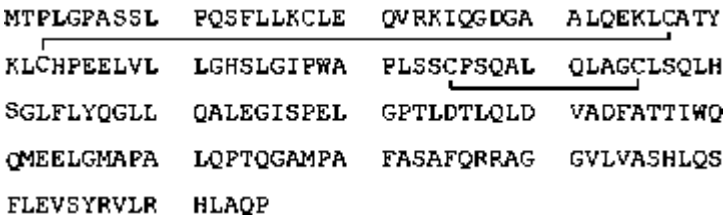
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Filgrastim Concentrated Solution

General Notices

(Ph. Eur. monograph 2206)



$C_{845}H_{1339}N_{223}O_{243}S_9$ 18 799 *121181-53-1*

Action and use

Recombinant methionyl human granulocyte colony-stimulating factor.

Ph Eur

DEFINITION

Solution of a protein having the primary structure of the 174-amino-acid isoform of human granulocyte colony-stimulating factor (huG-CSF) plus 1 additional amino acid, an *N*-terminal methionine. In contrast to its natural counterpart, the protein is not glycosylated. huG-CSF is produced and secreted by endothelial cells, monocytes and other immune cells. The protein stimulates the differentiation and proliferation of leucocyte stem cells into mature granulocytes.

Content

Minimum 0.9 mg of protein per millilitre.

Potency

Minimum 0.9×10^8 IU per milligram of protein.

PRODUCTION

Filgrastim concentrated solution is produced by a method based on recombinant DNA (rDNA) technology, using bacteria as host cells.

Prior to release, the following tests are carried out on each batch of filgrastim concentrated solution, unless exemption has been granted by the competent authority.

www.webofpharma.com

https://thuocngocanh.com/

Host-cell-derived proteins

The limit is approved by the competent authority.

Host-cell- or vector-derived DNA

The limit is approved by the competent authority.

CHARACTERS

Appearance

Clear, colourless or slightly yellowish liquid.

IDENTIFICATION

A. It shows the expected biological activity (see Assay).

B. Examine the electropherograms obtained in the test for impurities with charges differing from that of filgrastim.

Results The principal band in the electropherogram obtained with the test solution is similar in position to the principal band in the electropherogram obtained with reference solution (a).

C. Examine the chromatograms obtained in the test for impurities with molecular masses higher than that of filgrastim.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

D. Examine the electropherograms obtained under both reducing and non-reducing conditions in the test for impurities with molecular masses differing from that of filgrastim.

Results The principal band in the electropherogram obtained with test solution (a) is similar in position to the principal band in the electropherogram obtained with reference solution (b).

E. Examine the chromatograms obtained in the test for related proteins.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and shape to the principal peak in the chromatogram obtained with the reference solution.

F. Peptide mapping (*2.2.55*).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution Introduce a volume of the preparation to be examined corresponding to 25 µg of protein into a polypropylene tube. Add 25 µL of a 0.1 mg/mL solution of *glutamyl endopeptidase for peptide mapping R*. Dilute to 100 µL with *0.02 M sodium phosphate buffer solution pH 8.0 R*, stopper the tube and incubate at about 37 °C for 17 h. Cool to 2-8 °C until analysis.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *filgrastim CRS* instead of the preparation to be examined.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC SEPARATION. Liquid chromatography (2.2.29).

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm) with a pore size of 20 nm;

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: dilute 0.5 mL of *trifluoroacetic acid R* in 950 mL of *water for chromatography R*, add 50 mL of *acetonitrile for chromatography R* and mix;

— *mobile phase B*: dilute 0.5 mL of *trifluoroacetic acid R* in 50 mL of *water for chromatography R*, add 950 mL of *acetonitrile for chromatography R* and mix;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	97 → 94	3 → 6
8 - 25	94 → 66	6 → 34
25 - 40	66 → 10	34 → 90
40 - 45	10	90

Flow rate 0.2 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL.

System suitability The chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of filgrastim digest supplied with *filgrastim CRS*.

Results The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

TESTS

Impurities with molecular masses higher than that of filgrastim

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Solution A Dissolve 4.1 g of *sodium acetate R* in 400 mL of *water R*, adjust to pH 4.0 with *acetic acid R* and dilute to 500 mL with *water R*.

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dilute the preparation to be examined with solution A to obtain a concentration of 0.4 mg/mL.

Reference solution Dilute *filgrastim CRS* with solution A to obtain a concentration of 0.4 mg/mL.

Resolution solution Mix a sample of the reference solution for about 30 s using a vortex mixer.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5 µm) of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 10 000 to 500 000;

— *temperature*: 30 °C.

Mobile phase Dissolve 7.9 g of *ammonium hydrogen carbonate R* in 1000 mL of *water for chromatography R* and adjust to pH 7.0 with *phosphoric acid R*; dilute to 2000 mL with *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Relative retention With reference to the filgrastim monomer (retention time = about 19 min): aggregates = about 0.60; filgrastim oligomer 1 = about 0.75; filgrastim oligomer 2 = about 0.80; filgrastim dimer = about 0.85.

System suitability Resolution solution:

— *retention time*: filgrastim monomer = 17 min to 20 min;

— *resolution*: minimum 3 between the peaks due to the filgrastim dimer and the filgrastim monomer.

Calculate the percentage content of the dimer, oligomers and aggregates.

Limits:

— *impurities with molecular masses higher than that of filgrastim, other than the dimer*: maximum 0.5 per cent;

— *total of impurities with molecular masses higher than that of filgrastim*: maximum 2 per cent.

Impurities with molecular masses differing from that of filgrastim

Polyacrylamide gel electrophoresis (*2.2.31*) under both reducing and non-reducing conditions.

Gel dimensions 1 mm thick.

Resolving gel 13 per cent acrylamide.

Sample buffer (non-reducing conditions) Mix equal volumes of *water R* and *concentrated SDS-PAGE sample buffer R*.

www.webofpharma.com

https://thuocngocanh.com/

Sample buffer (reducing conditions) Mix equal volumes of *water R* and *concentrated SDS-PAGE sample buffer for reducing conditions R* containing 2-mercaptoethanol as the reducing agent.

Test solution (a) Dilute the preparation to be examined with sample buffer to obtain a concentration of 100 µg/mL.

Test solution (b) To 0.20 mL of test solution (a) add 0.20 mL of sample buffer.

Test solution (c) Dilute 0.20 mL of test solution (b) to 1 mL with sample buffer.

Test solution (d) Dilute 0.20 mL of test solution (c) to 1 mL with sample buffer.

Test solution (e) To 0.20 mL of test solution (d) add 0.20 mL of sample buffer.

Reference solution (a) Solution of molecular mass markers suitable for calibrating SDS-polyacrylamide gels in the range of 14.4-94 kDa.

Reference solution (b) Dilute *filgrastim CRS* with sample buffer to obtain a concentration of 100 µg/mL.

Sample treatment Boil for 5 min.

Application 20 µL.

Detection By silver staining.

System suitability:

— reference solution (a): the validation criteria are met;

— a band is seen in the electropherogram obtained with test solution (e);

— a gradation of intensity of staining is seen in the electropherograms obtained with test solutions (a) to (e).

Limit Test solution (a):

— *impurities with molecular masses lower or higher than that of filgrastim*: no band is more intense than the principal band in the electropherogram obtained with test solution (d) (2.0 per cent).

Impurities with charges differing from that of filgrastim

Isoelectric focusing (*2.2.54*).

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 0.3 mg/mL.

Reference solution (a) Dilute *filgrastim CRS* with *water R* to obtain a concentration of 0.3 mg/mL.

Reference solution (b) Dilute *filgrastim CRS* with *water R* to obtain a concentration of 0.03 mg/mL.

Reference solution (c) Use an isoelectric point (pI) calibration solution, in the pI range of 2.5-6.5, prepared according to the manufacturer's instructions.

Focusing:

www.webofpharma.com

https://thuocngocanh.com/

— *pH gradient*: 4.5-8.0;

— *catholyte*: 1 M solution of *sodium hydroxide R*;

— *anolyte*: 0.04 M solution of *glutamic acid R* in a 0.0025 per cent *V/V* solution of *phosphoric acid R*;

— *application*: 20 µL.

Detection As described in *2.2.54*.

System suitability:

— in the electropherogram obtained with reference solution (c), the relevant isoelectric point markers are distributed along the entire length of the gel;

— in the electropherogram obtained with reference solution (a), the pI of the principal band is 5.7 to 6.3.

Limit:

— *any impurity*: no band is more intense than the principal band in the electropherogram obtained with reference solution (b) (10 per cent).

Related proteins

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dilute the preparation to be examined with *water for chromatography R* to obtain a concentration of 0.5 mg/mL.

Reference solution (a) Dilute the content of a vial of *filgrastim CRS* with *water for chromatography R* to obtain a concentration of 0.5 mg/mL.

Reference solution (b) To 250 µL of reference solution (a), add 2.5 µL of a 4.5 g/L solution of hydrogen peroxide. Mix and incubate at 25 ± 2 °C for 30 min, then add 1.9 mg of *L-methionine R*.

Reference solution (c) To 250 µL of reference solution (a), add 0.25 mg of *dithiothreitol R*. Mix and incubate at 35 ± 2 °C for 60 min.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm;

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* in 1000 mL of *water for chromatography R*;

— *mobile phase B*: dilute 1 mL of *trifluoroacetic acid R* in 100 mL of *water for chromatography R*, then add 900 mL of *acetonitrile R*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	60 → 20	40 → 80
30 - 35	20	80
35 - 45	20 → 60	80 → 40

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 50 µL of the test solution and reference solutions (b) and (c).

Relative retention With reference to filgrastim (retention time = about 23 min): oxidised filgrastim (form 1) = about 0.84; oxidised filgrastim (form 2) = about 0.98; reduced filgrastim = about 1.04.

System suitability Reference solution (b):

— *symmetry factor*: maximum 1.8 for the peak due to filgrastim;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to oxidised filgrastim (form 2) and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to filgrastim.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to filgrastim and reduced filgrastim;

— *symmetry factor*: maximum 1.8 for the peak due to filgrastim.

Limits:

— *any impurity*: for each impurity, maximum 1.0 per cent;

— *total*: maximum 2.0 per cent.

Bacterial endotoxins (*2.6.14*)

Less than 2 IU in the volume that contains 1.0 mg of protein.

ASSAY

Protein

Liquid chromatography (*2.2.29*) as described in the test for related proteins with the following modification.

Injection Test solution and reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of filgrastim ($C_{845}H_{1339}N_{223}O_{243}S_9$) taking into account the assigned content of $C_{845}H_{1339}N_{223}O_{243}S_9$ in *filgrastim CRS*.

Potency

The potency of the preparation to be examined is determined by comparison of the dilutions of the test preparation with the dilutions of the International Standard of filgrastim or with a reference preparation calibrated in International Units.

The International Unit is the activity contained in a stated amount of the appropriate International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Carry out the assay using a suitable method such as the following, which uses the conversion of a tetrazolium salt (MTS) as a staining method. Alternative methods of quantifying cell proliferation, such as measurement of intracellular ATP by luciferase bioluminescence, have also been found suitable, and may be used as the assay readout, subject to appropriate validation. The assay conditions (for example, cell concentration, incubation time and dilution steps) are then adapted accordingly.

Use an established cell line responsive to filgrastim. M-NFS-60 cells (ATCC No. CRL-1838) that have been made sensitive to G-CSF have been found suitable. Incubate with varying dilutions of test and reference preparations of filgrastim. Then incubate with a solution of *tetrazolium salt R*. This cytochemical stain is converted by cellular dehydrogenases to a coloured formazan product. The formazan is then measured spectrophotometrically.

Add 50 µL of dilution medium to all wells of a 96-well microplate. Add an additional 50 µL of this solution to the wells designed for the blanks. Add 50 µL of each solution to be tested in triplicate (test preparation and reference preparation at a concentration of about 800 IU/mL, plus a series of 10 twofold dilutions to obtain a standard curve). Prepare a suspension of M-NFS-60 cells containing 7×10^5 cells per millilitre. Immediately before use, add 2-mercaptoethanol to a final concentration of 0.1 mM, and add 50 µL of the prepared cell suspension to each well, maintaining the cells in a uniform suspension during addition.

Incubate the plate at 36.0-38.0 °C for 44-48 h in a humidified incubator using 6 ± 1 per cent CO_2. Add 20 µL of a 5.0 g/L sterile solution of *tetrazolium salt R* to each well and reincubate for 4 h. Estimate the quantity of formazan produced using a microplate reader at 490 nm.

Calculate the potency of the preparation to be examined using a suitable statistical method, for example the parallel line assay (*5.3*).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 74 per cent and not more than 136 per cent of the estimated potency.

LABELLING

The label states:

— the content, in milligrams of protein per millilitre;

— the potency, in International Units per milligram of protein.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Filgrastim Injection

General Notices

(Ph. Eur. monograph 2848)

Action and use

Recombinant methionyl human granulocyte colony-stimulating factor.

Ph Eur

DEFINITION

Sterile solution for injection of a protein having the primary structure of the 174-amino-acid isoform of human granulocyte colony-stimulating factor (huG-CSF) plus 1 additional amino acid, an *N*-terminal methionine. In contrast to its natural counterpart, the protein is not glycosylated.

Content

90.0 per cent to 110.0 per cent of the amount of filgrastim stated on the label.

Potency

80 per cent to 125 per cent of the potency stated on the label when determined using the conditions described under Assay.

PRODUCTION

Filgrastim injection is prepared from *Filgrastim concentrated solution (2206)*.

The concentrated solution is diluted with a formulation buffer (acetate or glutamate) containing sodium hydroxide, sorbitol, and polysorbate 80 as excipients. This preparation is passed through a bacteria-retentive filter and distributed aseptically into the final containers. Where excipients or formulation buffer other than those mentioned above are used, their compatibility with the tests described hereafter must be confirmed.

CHARACTERS

Appearance

Clear, colourless or slightly yellowish liquid.

IDENTIFICATION

https://thuocngocanh.com/

A. It shows the expected biological activity (see Assay).

B. Examine the chromatograms obtained in the test for related proteins.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and shape to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

pH (2.2.3)

As approved by the competent authority.

Impurities with molecular masses higher than that of filgrastim

Size-exclusion chromatography (2.2.30): use the normalisation procedure.

Solution A Dissolve 4.1 g of *sodium acetate R* in 400 mL of *water R*, adjust to pH 4.0 with *acetic acid R* and dilute to 500 mL with *water R*.

Test solution Dilute the preparation to be examined with solution A to obtain a concentration of 0.4 mg/mL.

Reference solution Dilute *filgrastim CRS* with solution A to obtain a concentration of 0.4 mg/mL.

Resolution solution Mix a sample of the reference solution for about 30 s using a vortex mixer.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R* (5 µm) of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 10 000 to 500 000;

— *temperature*: 30 °C.

Mobile phase Dissolve 7.9 g of *ammonium hydrogen carbonate R* in 1000 mL of *water for chromatography R* and adjust to pH 7.0 with *phosphoric acid R*; dilute to 2000 mL with *water for chromatography R*.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Relative retention With reference to the filgrastim monomer (retention time = about 19 min): aggregates = about 0.60; filgrastim oligomer 1 = about 0.75; filgrastim oligomer 2 = about 0.80; filgrastim dimer = about 0.85.

System suitability Resolution solution:

— *retention time*: filgrastim monomer = 17 min to 20 min;

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 3.0 between the peaks due to the filgrastim dimer and the filgrastim monomer.

Calculate the percentage content of the dimer, oligomers and aggregates.

Limits:

— *impurities with molecular masses higher than that of filgrastim, other than the dimer*: maximum 0.5 per cent;

— *total of impurities with molecular masses higher than that of filgrastim*: maximum 1.0 per cent.

Impurities with charges differing from that of filgrastim

Isoelectric focusing (2.2.54) with the following modifications. *Prepare reference solutions (a), (b) and (c) immediately before loading on the gel.*

Gel concentration 5 per cent; commercially available gels may be used.

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 0.6 mg/mL.

Reference solution (a) Dilute *filgrastim CRS* with *water R* to obtain a concentration of 0.6 mg/mL.

Reference solution (b) To 10 µL of reference solution (a) add 190 µL of *water R* to obtain a concentration of 0.03 mg/mL.

Reference solution (c) To 10 µL of reference solution (a) add 490 µL of *water R* to obtain a concentration of 0.012 mg/mL.

Reference solution (d) Use an isoelectric point (pI) calibration solution, in the pI range of 3-10, prepared according to the manufacturer's instructions.

Focusing:

— *pH gradient*: a combination of ampholytes giving a functional separation in the pI range of 5.0-7.0;

— *catholyte*: 20 g/L solution of *sodium hydroxide R*;

— *anolyte*: 30 g/L solution of *glacial acetic acid R*;

— *application*: 15 µL.

Proceed with the isoelectric focusing by applying the electrical parameters according to the manufacturer's instructions. The following parameters have been found suitable for gels of dimensions 250 mm × 110 mm × 0.43 mm:

— *pre-focusing*: 700 V, 12 mA, 8 W, 20 min;

— *post-application*: 500 V, 8 mA, 8 W, 20 min;

— *focusing*: 2000 V, 14 mA, 14 W, 90 min;

— *final focusing*: 2500 V, 14 mA, 14 W, 10 min.

Detection Silver staining.

www.webofpharma.com

https://thuocngocanh.com/

Fixing solution A solution containing 36 g/L of *sulfosalicylic acid R* and 116 g/L of *trichloroacetic acid R*.

Sensitising solution Dissolve 17 g of *sodium acetate R* in about 100 mL of *water R*. Add 75 mL of *ethanol (96 per cent) R*, 10 mL of a 50 g/L solution of *anhydrous sodium thiosulfate R* and 1.25 mL of a 250 g/L solution of *glutaraldehyde R* and dilute to 250 mL with *water R*.

Silver solution Mix 100 µL of *formaldehyde solution R1* and 25 mL of a 25 g/L solution of *silver nitrate R* and dilute to 250 mL with *water R*.

Developing solution Dissolve 6.25 g of *sodium carbonate R* in about 200 mL of *water R*, add 50 µL of *formaldehyde solution R1* and dilute to 250 mL with *water R*.

Stopping solution Dissolve 3.65 g of *sodium edetate R* in 250 mL of *water R*.

Alternatively, commercially available staining kits may be used.

System suitability:

— in the electropherogram obtained with reference solution (d), the relevant isoelectric point markers are distributed along the entire length of the gel;

— in the electropherogram obtained with reference solution (c), the principal band is clearly visible.

Limits:

— maximum 7 bands of an intensity between that of the principal band in the electropherogram obtained with reference solution (c) (2 per cent) and that of the principal band in the electropherogram obtained with reference solution (b) (5 per cent) are present;

— no band has an intensity greater than that of the principal band in the electropherogram obtained with reference solution (b) (5 per cent).

Related proteins

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 0.5 mg/mL.

Reference solution (a) Dilute the contents of a vial of *filgrastim CRS* with *water R* to obtain a concentration of 0.5 mg/mL.

Reference solution (b) To 250 µL of reference solution (a), add 2.5 µL of a 4.5 g/L solution of hydrogen peroxide. Mix and incubate at 25 ± 2 °C for 30 min, then add 1.9 mg of *L-methionine R*.

Reference solution (c) To 250 µL of reference solution (a), add 0.25 mg of *dithiothreitol R*. Mix and incubate at 35 ± 2 °C for 60 min.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm;

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* in 1000 mL of *water for chromatography R*;

— *mobile phase B*: dilute 1 mL of *trifluoroacetic acid R* in 100 mL of *water for chromatography R*, then add 900 mL of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	60 → 20	40 → 80
30 - 35	20	80
35 - 45	20 → 60	80 → 40

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 50 µL of the test solution and reference solutions (b) and (c).

Relative retention With reference to filgrastim (retention time = about 23 min): oxidised filgrastim (form 1) = about 0.84; oxidised filgrastim (form 2) = about 0.98; reduced filgrastim = about 1.04.

System suitability Reference solution (b):

— *symmetry factor*: maximum 1.8 for the peak due to filgrastim;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to oxidised filgrastim (form 2) and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to filgrastim.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to filgrastim and reduced filgrastim;

— *symmetry factor*: maximum 1.8 for the peak due to filgrastim.

Limits:

— *any impurity*: for each impurity, maximum 3.0 per cent;

— *total*: maximum 6.5 per cent.

Osmolality (2.2.35)

As approved by the competent authority.

Bacterial endotoxins (2.6.14)

www.webofpharma.com

https://thuocngocanh.com/

Less than 10 IU in the volume that contains 1.0 mg of protein.

ASSAY

Protein

Liquid chromatography (2.2.29) as described in the test for related proteins with the following modification.

Injection Test solution and reference solution (a).

Calculate the content of filgrastim ($C_{845}H_{1339}N_{223}O_{243}S_9$) taking into account the assigned content of $C_{845}H_{1339}N_{223}O_{243}S_9$ in *filgrastim CRS*.

Potency

The potency of the preparation to be examined is determined by comparison of the dilutions of the test preparation with the dilutions of the International Standard of filgrastim or with a reference preparation calibrated in International Units.

The International Unit is the activity contained in a stated amount of the appropriate International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Carry out the assay using a suitable method such as the following, which uses the conversion of a tetrazolium salt (MTS) as a staining method. Alternative methods of quantifying cell proliferation, such as measurement of intracellular ATP by luciferase bioluminescence, have also been found suitable, and may be used as the assay readout, subject to appropriate validation. The assay conditions (for example, cell concentration, incubation time and dilution steps) are then adapted accordingly.

Use an established cell line responsive to filgrastim. M-NFS-60 cells (ATCC No. CRL-1838) that have been made sensitive to G-CSF have been found suitable. Incubate with varying dilutions of test and reference preparations of filgrastim. Then incubate with a solution of *tetrazolium salt R*. This cytochemical stain is converted by cellular dehydrogenases to a coloured formazan product. The formazan is then measured spectrophotometrically.

Add 50 µL of dilution medium to each well of a 96-well microplate. Add an additional 50 µL of this solution to the wells designed for the blanks. Add 50 µL of each solution to be tested in triplicate (test preparation and reference preparation at a concentration of about 800 IU/mL, plus a series of 10 twofold dilutions to obtain a standard curve). Prepare a suspension of M-NFS-60 cells containing 7×10^5 cells per millilitre. Immediately before use, add 2-mercaptoethanol to a final concentration of 0.1 mM, and add 50 µL of the prepared cell suspension to each well, maintaining the cells in a uniform suspension during addition.

Incubate the plate at 36.0-38.0 °C for 44-48 h in a humidified incubator using 6 ± 1 per cent CO_2. Add 20 µL of a 5.0 g/L sterile solution of *tetrazolium salt R* to each well and reincubate for 4 h. Estimate the quantity of formazan produced using a microplate reader at 490 nm.

Calculate the potency of the preparation to be examined using a suitable statistical method, for example the parallel line assay (5.3).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) are not less than 74 per cent and not more than 136 per cent of the estimated potency.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

In a sterile, airtight, tamper-evident container, protected from light, at a temperature of 2 °C to 8 °C.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

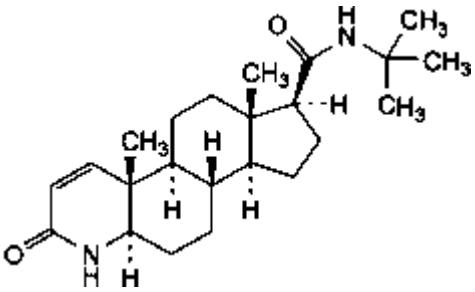
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Finasteride

General Notices

(Ph. Eur. monograph 1615)



$C_{23}H_{36}N_2O_2$ 372.6 *98319-26-7*

Action and use

5-Alpha reductase inhibitor; treatment of benign prostatic hyperplasia.

Preparation

Finasteride Tablets

Ph Eur

DEFINITION

N-(1,1-Dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *finasteride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Specific optical rotation (2.2.7)

+ 12.0 to + 14.0 (dried substance).

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R1*, *water for chromatography R* (50:50 *V/V*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dissolve 100.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of *finasteride CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *finasteride for peak identification CRS* (containing impurities A and C) in 1.0 mL of the solvent mixture.

Reference solution (c) Dilute 1.0 mL of test solution (b) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 60 °C.

Mobile phase *acetonitrile R1*, *tetrahydrofuran R*, *water for chromatography R* (10:10:80 *V/V/V*).

Flow rate 1.5 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 210 nm.

Injection 15 µL of test solution (b) and reference solutions (b) and (c).

Run time Twice the retention time of finasteride.

Identification of impurities Use the chromatogram supplied with *finasteride for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C.

Relative retention With reference to finasteride (retention time = about 28 min): impurity A = about 0.9; impurity C = about 1.3.

System suitability:

— *signal-to-noise ratio*: minimum 40 for the principal peak in the chromatogram obtained with reference solution (c);

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to finasteride in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 2.4;

— for each impurity, use the concentration of finasteride in reference solution (c).

Limits:

— *impurities A, C*: for each impurity, maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (a) and reference solution (a).

Calculate the percentage content of $C_{23}H_{36}N_2O_2$ taking into account the assigned content of *finasteride CRS*.

STORAGE

www.webofpharma.com

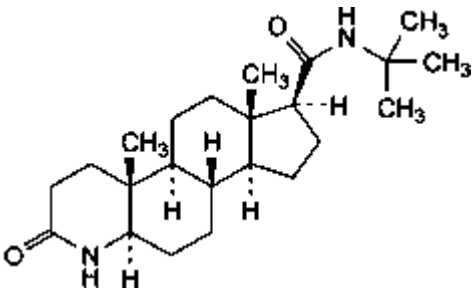
https://thuocngocanh.com/

Protected from light.

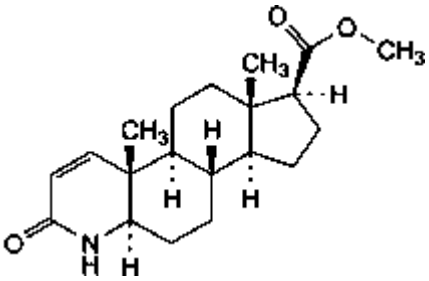
IMPURITIES

Specified impurities A, C.

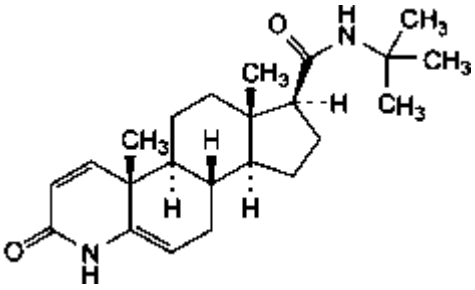
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B.



A. *N*-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (dihydrofinasteride),



B. methyl 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylate,



C. *N*-(1,1-dimethylethyl)-3-oxo-4-azaandrosta-1,5-diene-17β-carboxamide (Δ5-finasteride).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Finasteride Tablets

General Notices

Action and use

5-Alpha reductase inhibitor; treatment of benign prostatic hyperplasia.

DEFINITION

Finasteride Tablets contain Finasteride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of finasteride, $C_{23}H_{36}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the test for Dissolution, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to finasteride in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to finasteride in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 10 mL sample of the medium and filter. Use the filtered medium.

(2) A suitable solution of *finasteride BPCRS* in a mixture of 3 volumes of *water* and 7 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 220 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

21 volumes of *water* and 29 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak corresponding to finasteride is less than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{36}N_2O_2$ in the medium from the chromatograms obtained using the declared content of $C_{23}H_{36}N_2O_2$ in *finasteride BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 30 mL of a mixture of equal volumes of *acetonitrile* and *water* to a quantity of powdered tablets containing 100 mg of Finasteride, dilute to 50 mL with the same mixture of solvents, centrifuge and filter the supernatant liquid (0.2%).

(2) Dilute 2 volumes of solution (1) to 100 volumes with a mixture of equal volumes of *acetonitrile* and *water*, dilute 1 volume of this solution to 10 volumes with a mixture of equal volumes of *acetonitrile* and *water*.

(3) 0.2% w/v of *finasteride for peak identification EPCRS* in a mixture of equal volumes of *acetonitrile* and *water*.

(4) Dilute 25 volumes of solution (2) to 100 volumes with equal volumes of *acetonitrile* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *base-deactivated, end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 60°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

When the chromatograms are recorded using the prescribed conditions the retention time of finasteride is about 28 minutes. The retention times relative to finasteride are: impurity A, about 0.9; impurity B, about 1.2; impurity C, about 1.4. For solution (1) allow the chromatography to run for twice the retention time of the finasteride peak.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

10 volumes of *acetonitrile*, 10 volumes of *tetrahydrofuran* and 80 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid, unless in the chromatogram obtained with solution (3), the *peak-to-valley ratio* between finasteride impurity A and finasteride is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak due to finasteride impurity A and multiply the peak area by a correction factor of 2.4;

any peak corresponding to finasteride impurity A is not greater than 1.5 times the area of the principal peak in solution (2) (0.3%);

the area of any peak corresponding to finasteride impurity B is not greater than 1.5 times the area of the principal peak in solution (2) (0.3%);

the area of any peak corresponding to finasteride impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%).

Disregard any peak with an area less than 0.25 times the area of the peak due to finasteride in the chromatogram obtained with solution (2) (0.05%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Finasteride comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 3 volumes of *water* and 7 volumes of *acetonitrile* (solvent A).

(1) Add 2.5 mL of *water* to one tablet, shake with the aid of ultrasound until the tablet is completely dispersed. Add 35 mL of solvent A mix with the aid of ultrasound for a further 30 minutes. Cool to room temperature, dilute to 50 mL with solvent A, centrifuge and use the clear supernatant liquid.

(2) A suitable solution of *finasteride BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 45°.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Equal volumes of *acetonitrile* and 0.0025M of *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to finasteride is less than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{36}N_2O_2$ in each tablet using the declared content of $C_{23}H_{36}N_2O_2$ in *finasteride BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Finasteride

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Finasteride

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 3 volumes of *water* and 7 volumes of *acetonitrile* (solvent A).

(1) Add 25 mL of *water* to a quantity of the powdered tablets containing 50 mg of Finasteride, add 350 mL of solvent A, mix with the aid of ultrasound for 30 minutes. Allow to attain room temperature and dilute to 500 mL with solvent A, centrifuge and use the clear supernatant liquid.

(2) 0.010% w/v of *finasteride BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to finasteride is less than 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{36}N_2O_2$ in the tablets from the chromatograms obtained and using the declared content of $C_{23}H_{36}N_2O_2$ in *finasteride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Finasteride.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

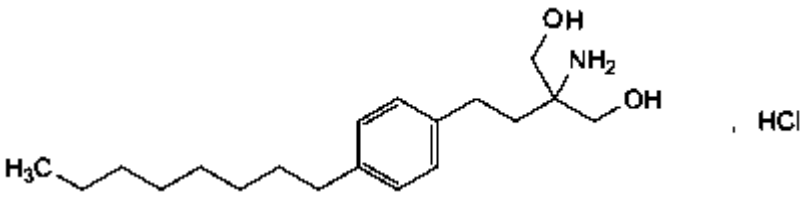
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fingolimod Hydrochloride

General Notices

(Ph. Eur. monograph 2988)



$C_{19}H_{34}ClNO_2$ 343.9 *162359-56-0*

Action and use

Sphingosine-1-phosphate receptor modulator; immunomodulator.

Ph Eur

DEFINITION

2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Mulls in *liquid paraffin R* if recording by transmission.

www.webofpharma.com

https://thuocngocanh.com/

Comparison *fingolimod hydrochloride CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (a) of chlorides (*2.3.1*).

If precipitation is observed after addition of *dilute nitric acid R*, centrifuge and use the supernatant in the remainder of the test.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R1*, 0.1 per cent *V/V* solution of *phosphoric acid R* (50:50 *V/V*).

Test solution Dissolve 30.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 30.0 mg of *fingolimod hydrochloride CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 3 mg of *fingolimod for system suitability CRS* (containing impurities C and G) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *encapsulated polar-embedded octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 22	80 → 5	20 → 95
22 - 25	5	95

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *fingolimod for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C and G.

Relative retention With reference to fingolimod (retention time = about 11 min): impurity G = about 1.08; impurity C = about 1.10.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities G and C.

Calculation of percentage contents:

— for each impurity, use the concentration of fingolimod hydrochloride in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.32)

Maximum 0.3 per cent, determined on 50.0 mg by direct sample introduction.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

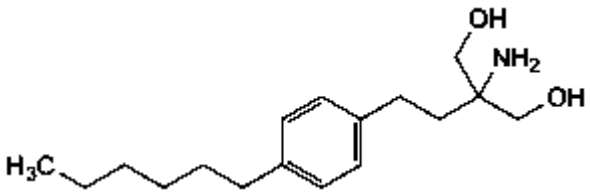
Calculate the percentage content of $C_{19}H_{34}ClNO_2$ taking into account the assigned content of *fingolimod hydrochloride CRS*.

IMPURITIES

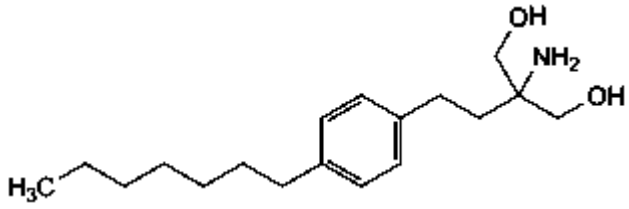
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, D, E, F, G, H, I.*

www.webofpharma.com

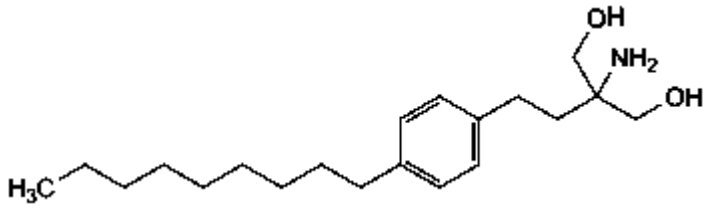
https://thuocngocanh.com/



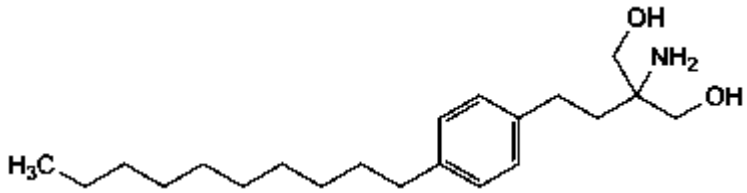
A. 2-amino-2-[2-(4-hexylphenyl)ethyl]propane-1,3-diol,



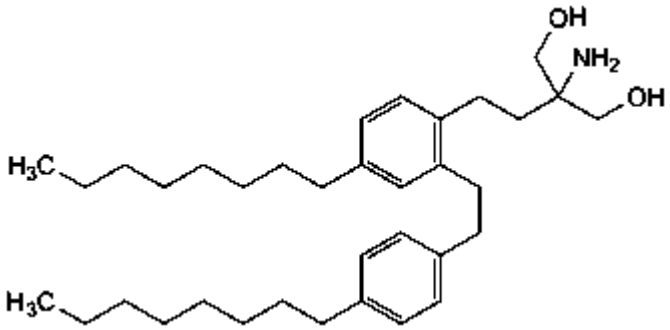
B. 2-amino-2-[2-(4-heptylphenyl)ethyl]propane-1,3-diol,



C. 2-amino-2-[2-(4-nonylphenyl)ethyl]propane-1,3-diol,



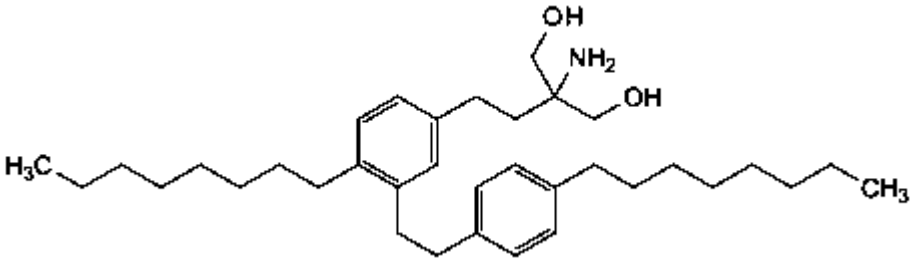
D. 2-amino-2-[2-(4-decylphenyl)ethyl]propane-1,3-diol,



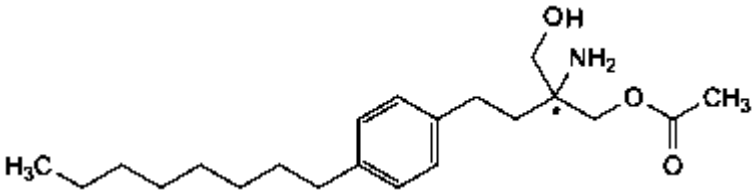
E. 2-amino-2-[2-[4-octyl-2-[2-(4-octylphenyl)ethyl]phenyl]ethyl]propane-1,3-diol,

www.webofpharma.com

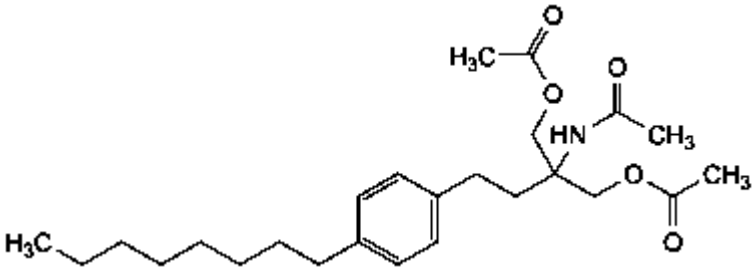
https://thuocngocanh.com/



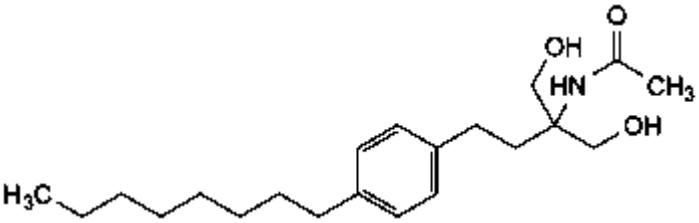
F. 2-amino-2-[2-[4-octyl-3-[2-(4-octylphenyl)ethyl]phenyl]ethyl]propane-1,3-diol,



G. (2Ξ)-2-amino-2-(hydroxymethyl)-4-(4-octylphenyl)butyl acetate,



H. 2-acetamido-2-[(acetyloxy)methyl]-4-(4-octylphenyl)butyl acetate,



I. *N*-[1-hydroxy-2-(hydroxymethyl)-4-(4-octylphenyl)butan-2-yl]acetamide.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Fish Oil, Rich in Omega-3-Acids

General Notices

(Ph. Eur. monograph 1912)

Ph Eur

DEFINITION

Purified, winterised and deodorised fatty oil obtained from fish of families such as *Engraulidae*, *Carangidae*, *Clupeidae*, *Osmeridae*, *Scombridae* and *Ammodytidae* (type I), or from the genera *Thunnus* and *Sarda* within the family *Scombridae* (type II). The omega-3 acids are defined as the following acids: *alpha*-linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA), heneicosapentaenoic acid (C21:5 n-3), clupanodonic acid (C22:5 n-3) and cervonic (docosahexaenoic) acid (C22:6 n-3; DHA).

Content

	Type I	Type II
EPA, expressed as triglycerides	minimum 13 per cent	4 per cent to 12 per cent
DHA, expressed as triglycerides	minimum 9 per cent	minimum 20 per cent
Total omega-3 acids, expressed as triglycerides	minimum 28 per cent	minimum 28 per cent

A suitable antioxidant may be added.

PRODUCTION

The content of dioxins and dioxin-like PCBs (polychlorinated biphenyls) is controlled using methods and limits in accordance with the requirements set in the European Union or other applicable regulations.

CHARACTERS

Appearance

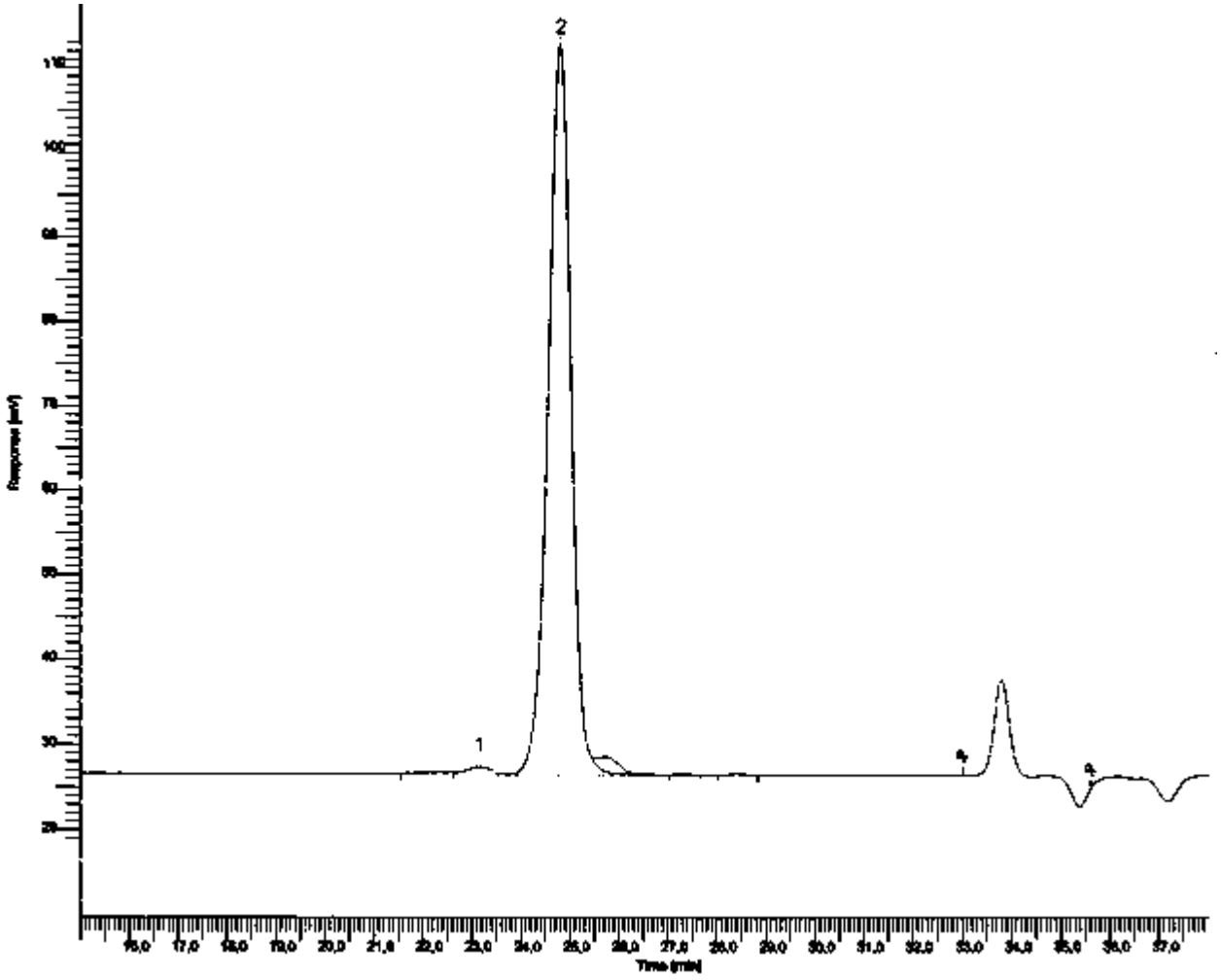
Pale yellow liquid.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, very soluble in acetone and in heptane, slightly soluble in anhydrous ethanol.



1. oligomers 2. triglycerides

Figure 1912.-1. – *Chromatogram for the test for oligomers in fish oil rich in omega-3 acids*

IDENTIFICATION

A. Examine the chromatograms obtained in the assay for EPA and DHA.

Results The peaks due to eicosapentaenoic acid methyl ester and docosahexaenoic acid methyl ester in the chromatogram obtained with test solution (b) are similar in retention time to the corresponding peaks in the chromatogram obtained with reference solutions (a_1) and (a_2).

B. It complies with the limits of the assay for EPA (type I or II).

TESTS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

The substance to be examined is not more intensely coloured than a reference solution prepared as follows: to 3.0 mL of red primary solution add 25.0 mL of yellow primary solution and dilute to 50.0 mL with a 10 g/L solution of *hydrochloric acid R* (*2.2.2, Method II*).

Absorbance (*2.2.25*)

Maximum 0.70 (type I) or maximum 0.50 (type II), at 233 nm.

Dilute 0.300 g of the substance to be examined to 50.0 mL with *trimethylpentane R*. Dilute 2.0 mL of the solution to 50.0 mL with *trimethylpentane R*.

Acid value (*2.5.1*)

Maximum 0.5, determined on 20.0 g in 50 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *ether R*.

Anisidine value (*2.5.36*)

Maximum 30.0 (type I) or maximum 15.0 (type II).

Peroxide value (*2.5.5, Method A*)

Maximum 10.0 (type I) or maximum 5.0 (type II).

Unsaponifiable matter (*2.5.7*)

Maximum 1.5 per cent, determined on 5.0 g.

Stearin

Immerse at least 10 mL of the substance to be examined previously at room temperature, for 3 h in a bath of iced water or a thermostatically controlled bath at 0 ± 0.5 °C. The sample remains clear.

Oligomers

Size-exclusion chromatography (*2.2.30*).

Test solution Dilute 50.0 mg of the substance to be examined to 10.0 mL with *tetrahydrofuran R*.

Reference solution In a 100 mL volumetric flask, dissolve 50 mg of *monodocosahexaenoin R*, 30 mg of *didocosahexaenoin R* and 20 mg of *tridocosahexaenoin R* in *tetrahydrofuran R* and dilute to 100.0 mL with the same solvent.

Column 3 columns to be connected in series:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with the following pore sizes:

— *column 1*: 50 nm;

— *column 2*: 10 nm;

www.webofpharma.com

https://thuvienthuocngocanh.com/

— *column 3*: 5 nm;

— *connection sequence*: injector – column 1 – column 2 – column 3 – detector.

Mobile phase tetrahydrofuran R.

Flow rate 0.8 mL/min.

Detection Differential refractometer.

Injection 40 µL.

System suitability Reference solution:

— *elution order*: tridocosahexaenoin, didocosahexaenoin, monodocosahexaenoin;

— *resolution*: minimum 2.0 between the peaks due to didocosahexaenoin and monodocosahexaenoin and minimum 1.0 between the peaks due to tridocosahexaenoin and didocosahexaenoin.

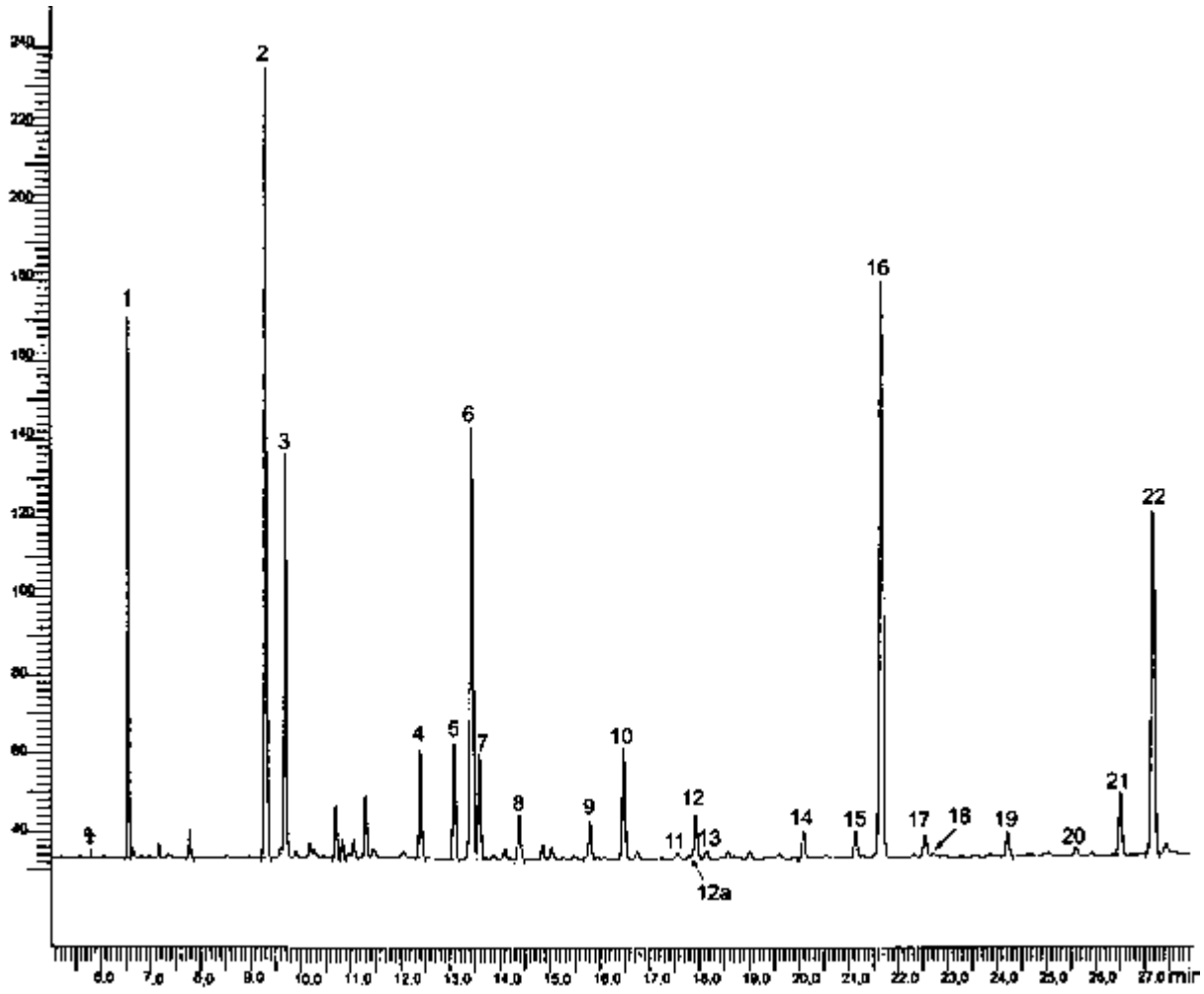
Identify the peaks from the chromatogram (Figure 1912.-1). Calculate the percentage content of oligomers using the following expression:

$$\frac{B}{A} \times 100$$

A	=	sum of the areas of all the peaks in the chromatogram;
B	=	area of the peak with a retention time less than the retention time of the triglyceride peak.

www.webofpharma.com

https://thuocngocanh.com/



1. C14:0	4. C16:4 n-1	7. C18:1 n-7	10. C18:4 n-3	12a. C20:1 n-11	15. C20:4 n-3	18. C22:1 n-9	21. C22:5 n-3
2. C16:0	5. C18:0	8. C18:2 n-6	11. C20:0	13. C20:1 n-7	16. C20:5 n-3	19. C21:5 n-3	22. C22:6 n-3
3. C16:1 n-7	6. C18:1 n-9	9. C18:3 n-3	12. C20:1 n-9	14. C20:4 n-6	17. C22:1 n-11	20. C22:5 n-6	

Figure 1912.-2. – *Chromatogram for the assay of total omega-3 acids in fish oil rich in omega-3 acids*

Limit:

— *oligomers*: maximum 1.5 per cent.

ASSAY

EPA and DHA (2.4.29)

For identification of the peaks, see Figure 1912.-2.

Total omega-3 acids (2.4.29)

See Figure 1912.-2.

www.webofpharma.com

https://thuocngocanh.com/

STORAGE

Under an inert gas, in a well-filled, airtight container, protected from light.

LABELLING

The label states:

— the concentration of EPA, DHA and total omega-3 acids, expressed as triglycerides;

— the type of fish oil rich in omega-3 acids (type I or II).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

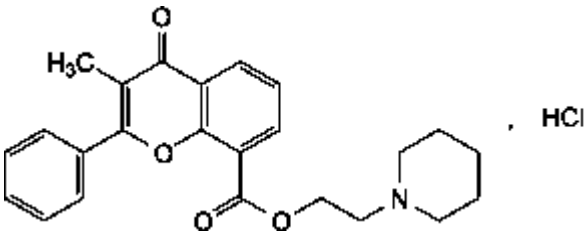
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flavoxate Hydrochloride

General Notices

(Ph. Eur. monograph 1692)



$C_{24}H_{26}ClNO_4$ 427.9 *3717-88-2*

Action and use

Anticholinergic.

Preparation

Flavoxate Tablets

Ph Eur

DEFINITION

2-(Piperidin-1-yl)ethyl 3-methyl-4-oxo-2-phenyl-4*H*-1-benzopyran-8-carboxylate hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flavoxate hydrochloride CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Use freshly prepared solutions.*

Solvent mixture Mix 20 volumes of a 0.4 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R* and 80 volumes of *acetonitrile R*.

Test solution Dissolve 10.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 6.0 mg of *flavoxate impurity A CRS* and 3.0 mg of *flavoxate impurity B CRS* in the solvent mixture, add 2.0 mL of the test solution and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 0.435 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 7.5 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	20	80
10 - 20	20 → 10	80 → 90
20 - 25	10	90

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 10 µL.

Relative retention With reference to flavoxate (retention time = about 10 min): impurity A = about 0.2; impurity B = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to impurity B and flavoxate.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total of unspecified impurities*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.350 g in 10 mL of *anhydrous formic acid R* and add 40 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 42.79 mg of $C_{24}H_{26}ClNO_4$.

STORAGE

Protected from light.

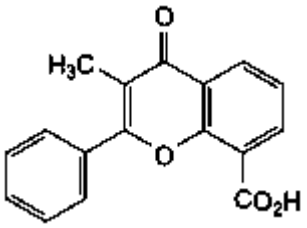
IMPURITIES

Specified impurities *A, B.*

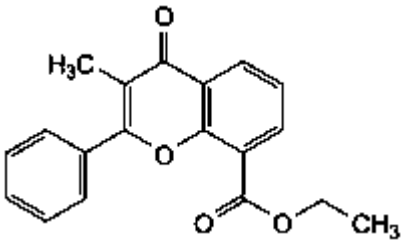
www.webofpharma.com

https://thuocngocanh.com/

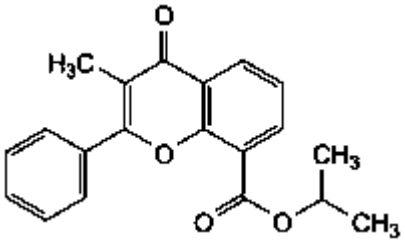
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



A. 3-methyl-4-oxo-2-phenyl-4*H*-1-benzopyran-8-carboxylic acid,



B. ethyl 3-methyl-4-oxo-2-phenyl-4*H*-1-benzopyran-8-carboxylate,



C. 1-methylethyl 3-methyl-4-oxo-2-phenyl-4*H*-1-benzopyran-8-carboxylate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flavoxate Tablets

General Notices

Action and use

Anticholinergic.

DEFINITION

Flavoxate Tablets contain Flavoxate Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of flavoxate hydrochloride, $C_{24}H_{25}NO_4$,HCl

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 0.2 g of Flavoxate Hydrochloride with 10 mL of *dichloromethane*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of flavoxate hydrochloride *(RS 143)*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (5) corresponds to that in the chromatogram obtained with solution (6).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.2 g of Flavoxate Hydrochloride with 10 mL of *chloroform* and filter.

(2) 0.03% w/v of *flavoxate impurity A EPCRS* in *chloroform*.

(3) 0.015% w/v of *flavoxate impurity B EPCRS* in *chloroform*.

(4) Dilute 1 volume of solution (1) to 500 volumes with *chloroform*.

(5) Dilute 1 volume of solution (1) to 20 volumes with *chloroform*.

(6) 0.1% w/v of *flavoxate hydrochloride BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 50 µL of solution (1). Apply 10 µL of solutions (2), (3), (5), and (6). Apply 25 µL of solution (4).

www.webofpharma.com

https://thuocngocanh.com/

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 18M *ammonia*, 80 volumes of *propan-2-ol* and 200 volumes of *ethyl acetate*.

LIMITS

Any spot corresponding to impurity B in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3) (0.15%);

any other *secondary spot* in the chromatogram obtained with solution (1), other than the spot corresponding to impurity A, is not more intense than the spot in the chromatogram obtained with solution (4) (0.1%).

Impurity A

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.2 g of Flavoxate Hydrochloride with 10 mL of *chloroform* and filter.

(2) 0.01% w/v solution of *flavoxate impurity A EPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254} (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution (1).

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air and spray with *dilute potassium iodobismuthate solution*.

MOBILE PHASE

4 volumes of *glacial acetic acid*, 25 volumes of *ethyl acetate* and 70 volumes of *cyclohexane*.

LIMITS

Any spot corresponding to impurity A in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and finely powder 20 tablets. To a quantity of the powdered tablets containing 1 g of Flavoxate Hydrochloride add 600 mL of 0.1M *hydrochloric acid* and disperse with the aid of ultrasound for 10 minutes. Place in a water bath at 70° for 90 minutes, cool, add sufficient 0.1 M *hydrochloric acid* to produce 1 litre and filter. Dilute 5 mL to 250 mL with 0.1M *hydrochloric acid* and measure the *absorbance* of the resulting solution at 293 nm, Appendix II B. Calculate the content of $C_{24}H_{25}NO_4$,HCl from the absorbance obtained by repeating the measurement using a 0.002% w/v solution of *flavoxate hydrochloride BPCRS* in 0.1M *hydrochloric acid* *and* from the declared content of $C_{24}H_{25}NO_4$,HCl in *flavoxate hydrochloride BPCRS*.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Flavoxate Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and B listed under Flavoxate Hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

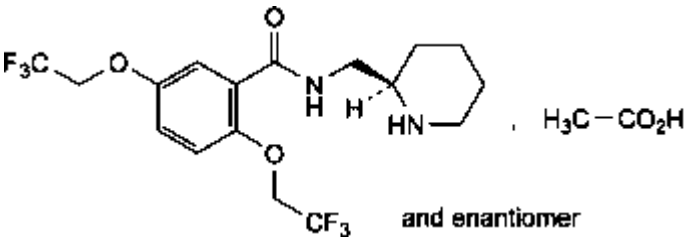
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flecainide Acetate

General Notices

(Ph. Eur. monograph 1324)



$C_{19}H_{24}F_6N_2O_5$ 474.4 *54143-56-5*

Action and use

Class I antiarrhythmic.

Preparations

Flecainide Injection

Flecainide Tablets

Ph Eur

DEFINITION

N-[(*RS*)-(Piperidin-2-ylmethyl)]-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic, crystalline powder.

Solubility

Soluble in water and in anhydrous ethanol. It is freely soluble in dilute acetic acid and practically insoluble in dilute hydrochloric acid.

IDENTIFICATION

www.webofpharma.com

https://thietbiuocngocanh.com/

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D.

A. Melting point (2.2.14): 146 °C to 152 °C, with a melting range not greater than 3 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50 mg in *ethanol (96 per cent) R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *ethanol (96 per cent) R*.

Spectral range 230-350 nm.

Absorption maximum At 298 nm.

Specific absorbance at the absorption maximum 61 to 65.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *flecainide acetate CRS*.

D. It gives reaction (b) of acetates (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.50 g in *water R*, add 0.1 mL of *glacial acetic acid R* and dilute to 20 mL with *water R*.

pH (2.2.3)

6.7 to 7.1.

Dissolve 0.25 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Impurity B

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in *methanol R* and dilute to 2.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of *flecainide impurity B CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b) Dissolve 0.10 g of the substance to be examined in reference solution (a) and dilute to 2.0 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Freshly prepared mixture of 5 volumes of *concentrated ammonia R* and 95 volumes of *acetone R*.

Application 5 µL.

Development Over 1/2 of the plate.

Drying At 100-105 °C until the ammonia has evaporated.

Detection Examine in ultraviolet light at 254 nm to establish the position of the flecainide spot, then spray with a freshly prepared 2 g/L solution of *ninhydrin R* in *methanol R* and heat at 100-110 °C for 2-5 min; examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity B*: any spot due to impurity B is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.2 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.25 g of the substance to be examined in *methanol R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *flecainide impurity A CRS* in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution (c) Dissolve 5 mg of *flecainide for system suitability CRS* (containing impurities C, D and E) in 1.0 mL of *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 2 mL of *concentrated ammonia R*, 4 mL of *triethylamine R* and 985 mL of *water R*; add 6 mL of *phosphoric acid R* and adjust to pH 2.8 with *concentrated ammonia R*;

— *mobile phase B*: *acetonitrile R*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	90	10
5 - 17	90 → 30	10 → 70
17 - 22	30	70

If a suitable baseline cannot be obtained, use another grade of triethylamine.

Flow rate 2 mL/min.

Detection Spectrophotometer at 300 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *flecainide for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C, D, and E; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to flecainide (retention time = about 11 min): impurity C = about 0.9; impurity A = about 1.1; impurity E = about 1.28; impurity D = about 1.32.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities E and D.

Limits:

— *impurities A, C, D, E*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 60 °C at a pressure not exceeding 0.6 kPa for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.400 g in 25 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

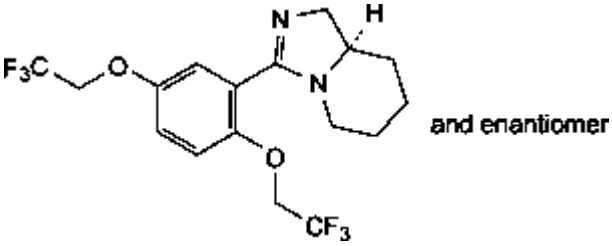
1 mL of *0.1 M perchloric acid* is equivalent to 47.44 mg of $C_{19}H_{24}F_6N_2O_5$.

STORAGE

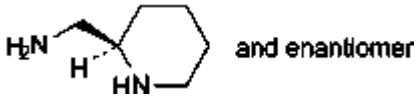
In an airtight container, protected from light.

IMPURITIES

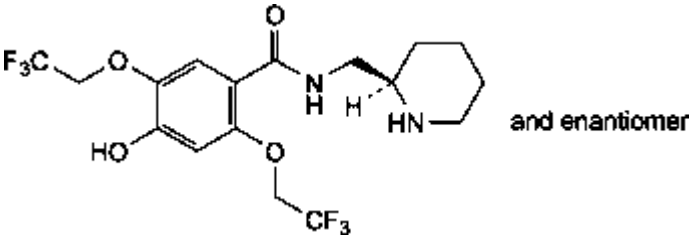
Specified impurities *A, B, C, D, E.*



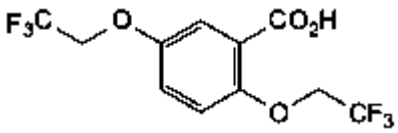
A. (8a*RS*)-3-[2,5-bis(2,2,2-trifluoroethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo[1,5-*a*]pyridine,



B. (*RS*)-(piperidin-2-yl)methanamine,



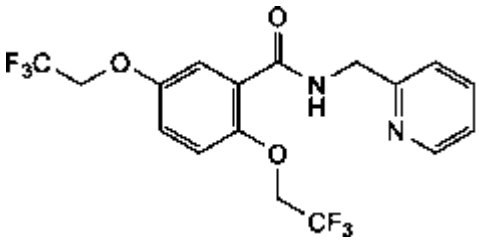
C. (*RS*)-4-hydroxy-*N*-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide,



D. 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid,

www.webofpharma.com

https://thuocngocanh.com/



E. *N*-(pyridin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flecainide Injection

General Notices

Action and use

Class I antiarrhythmic.

DEFINITION

Flecainide Injection is a sterile solution of Flecainide Acetate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of flecainide acetate, $C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless or almost colourless solution.

IDENTIFICATION

A. The *light absorption*, Appendix II B, of the solution obtained in the Assay in the range 230 nm to 350 nm exhibits a maximum at 296 nm.

B. In the test for (Piperidin-2-yl)methanamine, examine the chromatograms under *ultraviolet light (254 nm)* before spraying. The principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (3).

TESTS

Acidity

pH, 5.0 to 6.5, Appendix V L.

(Piperidin-2-yl)methanamine

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck plates are suitable) and a mixture of 2 volumes of *methanol*, 5 volumes of 18M *ammonia*, 100 volumes of *acetone* and 100 volumes of *dichloromethane* as the mobile phase but allowing the solvent front to ascend 10 cm above the line of application. Apply separately to the plate 1 µL of solution (1) and 5 µL of each of solutions (2) and (3). Solution (1) contains 0.025% w/v of *flecainide acetate impurity B EPCRS* [(piperidin-2-yl)methanamine] in *methanol*. For solution (2) dilute the injection, if necessary, with *methanol* to contain 1% w/v of flecainide acetate. Solution (3) contains 1% w/v of *flecainide acetate BPCRS* in *methanol*. After removal of the plate, allow it to dry in air and examine under

www.webofpharma.com

https://thuocngocanh.com/

ultraviolet light (254 nm) (for Identification test B). Spray the plate with a freshly prepared 0.2% w/v solution of *ninhydrin* in *methanol*, heat the plate at 105° for approximately 5 minutes and examine immediately. In the chromatogram obtained with solution (2) any bluish-purple spot corresponding to (piperidin-2-yl)methanamine is not more intense than the spot in the chromatogram obtained with solution (1) (0.5%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) is the injection diluted, if necessary, with a mixture of 29 volumes of *acetonitrile* and 71 volumes of *water* to contain 1.0% w/v of flecainide acetate. For solution (2) dilute 1 volume of solution (1) to 100 volumes with a mixture of 29 volumes of *acetonitrile* and 71 volumes of *water* and further dilute 1 volume of this solution to 5 volumes with the same solvent mixture. Solution (3) contains 0.01% w/v of each of *flecainide acetate BPCRS* and *flecainide impurity A EPCRS* in a mixture of 29 volumes of *acetonitrile* and 71 volumes of *water*.

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Zorbax C8 is suitable), (b) as the mobile phase with a flow rate of 2 mL per minute a mixture of 5 volumes of 1M *tetrabutylammonium hydroxide*, 10 volumes of *glacial acetic acid*, 290 volumes of *acetonitrile* and 710 volumes of *water*, the mixture adjusted to pH 5.8 using 18M *ammonia*, and (c) a detection wavelength of 254 nm.

Inject 20 µL of each solution. The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks corresponding to flecainide and flecainide impurity A is at least 3.5.

For solution (1) allow the chromatography to proceed for nine times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.2%) and the sum of the areas of any such peaks is not greater than two and a half times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.05 times the area of the peak in the chromatogram obtained with solution (2) (0.01%).

ASSAY

Dilute the injection with a 0.2% v/v solution of *lactic acid* to produce a solution containing 0.01% w/v of flecainide acetate and measure the *absorbance* of the resulting solution at the maximum at about 296 nm, Appendix II B, using a 0.2% v/v solution of *lactic acid* in the reference cell. Calculate the content of $C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$ in the injection from the *absorbance* obtained with a solution containing 0.01% w/v of *flecainide acetate BPCRS* in a 0.2% v/v solution of *lactic acid* and using the declared content of $C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$ in *flecainide acetate BPCRS*.

STORAGE

Flecainide Injection should not be allowed to freeze.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and D stated under Flecainide Acetate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flecainide Tablets

General Notices

Action and use

Class I antiarrhythmic.

DEFINITION

Flecainide Tablets contain Flecainide Acetate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of flecainide acetate, $C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, of the solution obtained in the Assay in the range 230 nm to 350 nm exhibits a maximum at 296 nm.

B. Shake a quantity of the powdered tablets containing 0.1 g of flecainide acetate with 10 mL of *methanol* for 10 minutes, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of flecainide acetate *(RS 397)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *0.1M hydrochloric acid* and rotate the paddle at 100 revolutions per minute. Withdraw a sample of 5 mL of the medium, filter and dilute the filtered solution, if necessary, with sufficient *0.1M hydrochloric acid* to produce a solution expected to contain about 0.005% w/v of flecainide acetate. Measure the *absorbance* of the solution at the maximum at 298 nm, Appendix II B, using 0.1M *hydrochloric acid* in the reference cell. Calculate the total content of flecainide acetate, $C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$, in the medium from the absorbance of a 0.005% w/v solution of *flecainide acetate BPCRS* in *0.1M hydrochloric acid* using the declared content of $C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$ in *flecainide acetate BPCRS*.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel F_{254} plate* (Merck plates are suitable) and a mixture of 2 volumes of *methanol*, 5 volumes of 18M *ammonia*, 100 volumes of *acetone* and 100 volumes of *dichloromethane* as the mobile

www.webofpharma.com

https://thuocngocanh.com/

phase but allowing the solvent front to ascend 10 cm above the line of application. Apply separately to the plate 1 µL of each of the following solutions. For solution (1) add 2 mL of *methanol* to a quantity of the powdered tablets containing 0.2 g of flecainide acetate, shake, centrifuge and use the supernatant liquid. Solution (2) contains 0.05% w/v of *flecainide acetate BPCRS* in *methanol*. Solution (3) contains 0.05% w/v of *flecainide impurity A EPCRS* in *methanol*. Solution (4) contains 0.02% w/v of *flecainide impurity B EPCRS* in *methanol*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to 3-[2,5-bis(2,2,2-trifluoroethoxy)phenyl]-1,5,6,7,8,8ahexahydroimidazo[1,5-*a*]pyridine (impurity A) is not more intense than the principal spot in the chromatogram obtained with solution (3) (0.5%). Spray the plate with a freshly prepared 0.2% w/v solution of *ninhydrin* in *absolute ethanol*, heat the plate at 105° for approximately 5 minutes and examine immediately. In the chromatogram obtained with solution (1) any bluish-purple spot corresponding to (piperidin-2-yl)methanamine (impurity B) is not more intense than the principal spot in the chromatogram obtained with solution (4) (0.2%) and any other *secondary spot* is not more intense than the principal spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Shake 20 tablets with 100 mL of a 2% v/v solution of *lactic acid* until the tablets have disintegrated, add 650 mL of *water*, shake with the aid of ultrasound for 30 minutes, add sufficient *water* to produce 1000 mL, mix and filter (Whatman GF/F paper is suitable), discarding the first 100 mL of filtrate. Dilute the filtrate with a 0.2% v/v solution of *lactic acid* to produce a solution containing 0.01% w/v of flecainide acetate and measure the *absorbance* of the resulting solution at the maximum at about 296 nm, Appendix II B, using a 0.2% v/v solution of *lactic acid* in the reference cell. Calculate the content of $C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$ in the tablets from the *absorbance* obtained with a solution containing 0.01% w/v of *flecainide acetate BPCRS* in a 0.2% v/v solution of *lactic acid* and using the declared content of $C_{17}H_{20}F_6N_2O_3,C_2H_4O_2$ in *flecainide acetate BPCRS*.

STORAGE

Flecainide Tablets should be stored at a temperature not exceeding 30°.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and D stated under Flecainide Acetate.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flexible Collodion

General Notices

Action and use

Skin protective.

DEFINITION

Flexible Collodion is a solution of Colophony in a mixture of Virgin Castor Oil and Collodion.

Extemporaneous preparation

The following formula and directions apply.

Colophony	25 g
Virgin Castor Oil	25 g
Collodion	Sufficient to produce 1000 mL

Mix the ingredients and stir until the colophony has dissolved; allow any deposit to settle and decant the clear liquid.

Flexible collodion complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements.

IDENTIFICATION

A. Expose a thin layer to the air. A thin, tenacious film is left which, when ignited, burns rapidly with a yellow flame.

B. Mix with an equal volume of *water*. A white, viscid, stringy mass is obtained.

Ethanol content

20 to 23% when determined by the following method.

Carry out the method for *gas chromatography*, Appendix III B using the following solutions in *ether*.

(1) 5% v/v of *absolute ethanol* and 5% v/v of *acetonitrile* (internal standard).

(2) 20% v/v of the substance being examined.

(3) 20% v/v of the substance being examined and 5% v/v of the internal standard.

CHROMATOGRAPHIC CONDITIONS

(a) Use a glass column (1.5 m × 4 mm) packed with porous polymer beads (100 to 120 mesh) (Porapak Q is suitable).

(b) Use *nitrogen* as the carrier gas at 40 mL per minute.

(c) Use isothermal conditions maintained at 120°.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use a flame ionisation detector.

(e) Inject 1 µL of each solution.

DETERMINATION OF CONTENT

Calculate the content of C_2H_6O from the areas of the peaks due to ethanol and *acetonitrile* in the chromatograms obtained with solution (1) and solution (3).

For preparations in which industrial methylated spirit has been used, determine the content of ethanol as described above.

Determine the concentration of methanol in the following manner. Carry out the chromatographic procedure described above but using the following solutions.

(1) 0.25% v/v of *methanol* and 0.25% v/v of *acetonitrile* (internal standard).

(2) Dilute a volume of the preparation being examined with *ether* to contain between 0.2% and 0.3% v/v of *methanol*.

(3) Prepare in the same manner as solution (2) but adding sufficient of the internal standard to produce a final concentration of 0.25% v/v.

LIMITS

The sum of the contents of ethanol and methanol is 20 to 23% v/v and the ratio of the content of methanol to that of ethanol is commensurate with industrial methylated spirit having been used.

COLLODION FOR THE PREPARATION OF FLEXIBLE COLLODION

DEFINITION

Collodion is a solution of Pyroxylin in a mixture of Ether and Ethanol (90 per cent).

PRODUCTION

It may be prepared by adding 100 g of pyroxylin to 900 mL of a mixture of 3 volumes of solvent ether and 1 volume of ethanol (90 per cent) and agitating continuously until dissolved. The viscosity of the resulting solution is determined and the solution is diluted with the solvent mixture until it complies with the requirement for kinematic viscosity.

In making Collodion the ethanol (90 per cent) may be replaced by industrial methylated spirit diluted so as to be of equivalent alcoholic strength, provided that the law and the statutory regulations governing the use of industrial methylated spirit are observed.

CHARACTERISTICS

A clear, viscid, colourless or pale straw-coloured liquid.

TESTS

Weight per mL

0.785 to 0.795 g, Appendix V G.

www.webofpharma.com

https://thuocngocanh.com/

Kinematic viscosity

405 to 700 $mm^2\ s^{-1}$, when determined using a falling sphere viscometer complying with British Standard 188: 1977 (Methods for the determination of viscosity of liquids). Fill the fall tube with the collodion to about 10 mm above the 220 mm mark, place vertically in the bath and allow to stand for air bubbles to clear and for temperature equilibrium to be attained. Clean the sphere, immerse it in a portion of the liquid being examined maintained at a temperature of 19.9° to 20.1° and when it is at this temperature introduce it, without wiping, into the delivery tube. Observe the time for the lowest part of the sphere to pass through the planes of the tops of the 175-mm mark and the 25-mm mark, using a telescope or other suitable device to avoid errors due to parallax. The average of three readings concordant to within 0.5% is taken as the time of fall. Calculate the kinematic viscosity (v) in square millimetres per second ($mm^2\ s^{-1}$) from the expression:

$$\nu = \frac{d^2 g(\delta - \rho)}{0.18 v \rho} \times 0.867$$

where	d	=	the diameter of the sphere in cm,
	δ	=	density of the sphere in $g\ cm^{-3}$,
	ρ	=	density of the collodion being examined in $g\ cm^{-3}$,
	v	=	velocity of the fall in $cm\ s^{-1}$,
	g	=	local acceleration due to gravity in $cm\ s^{-2}$.

When Collodion is prescribed or demanded, Flexible Collodion shall be dispensed or supplied.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

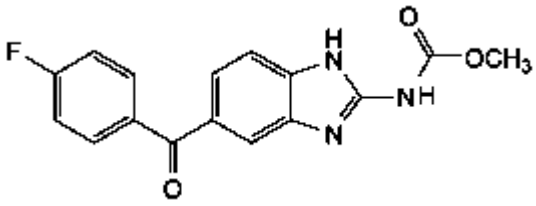
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Flubendazole

General Notices

(Ph. Eur. monograph 1721)



$C_{16}H_{12}FN_3O_3$ 313.3 *31430-15-6*

Action and use

Benzimadazole antihelminthic.

Ph Eur

DEFINITION

Methyl [5-(4-fluorobenzoyl)-1*H*-benzimidazol-2-yl]carbamate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, in ethanol (96 per cent) and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24), without recrystallisation.

Comparison *flubendazole CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *dimethylformamide R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *flubendazole for system suitability CRS* in *dimethylformamide R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *dimethylformamide R*. Dilute 5.0 mL of this solution to 20.0 mL with *dimethylformamide R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm,

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm),

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: 7.5 g/L solution of *ammonium acetate R*,

— *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	90 → 75	10 → 25
15 - 30	75 → 45	25 → 55
30 - 32	45 → 10	55 → 90
32 - 37	10	90

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

System suitability Reference solution (a):

www.webofpharma.com

https://thuocngocanh.com/

— the chromatogram obtained is similar to the chromatogram supplied with *flubendazole for system suitability CRS*.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.4; impurity C = 1.3; impurity D = 1.3; impurity G = 1.4,

— *impurities A, B, C, D, E, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent),

— *impurity F*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *any other impurity with a relative retention between 1.2 and 1.3*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent),

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent),

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C, for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 3 mL of *anhydrous formic acid R* and add 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 31.33 mg of $C_{16}H_{12}FN_3O_3$.

STORAGE

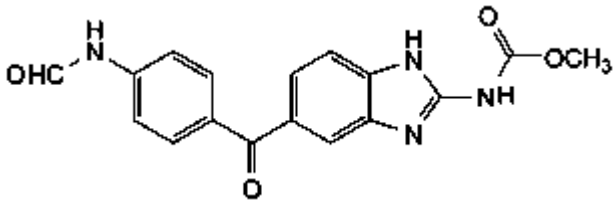
Protected from light.

IMPURITIES

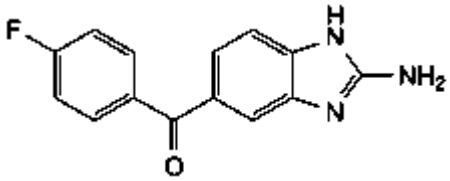
Specified impurities *A, B, C, D, E, F, G.*

www.webofpharma.com

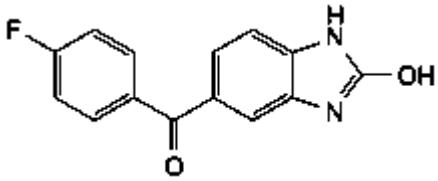
https://thuocngocanh.com/



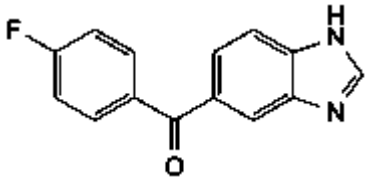
A. methyl [5-[4-(formylamino)benzoyl]-1*H*-benzimidazol-2-yl]carbamate,



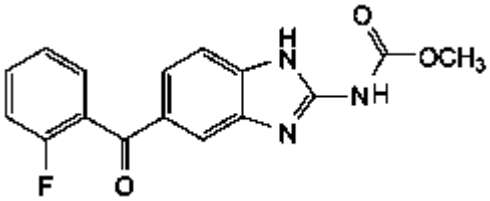
B. (2-amino-1*H*-benzimidazol-5-yl)(4-fluorophenyl)methanone,



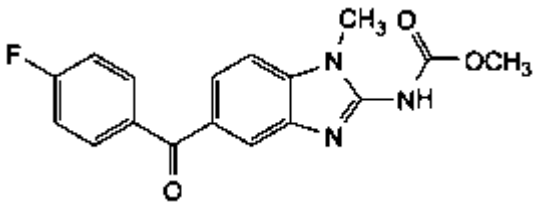
C. (4-fluorophenyl)(2-hydroxy-1*H*-benzimidazol-5-yl)methanone,



D. (1*H*-benzimidazol-5-yl)(4-fluorophenyl)methanone,



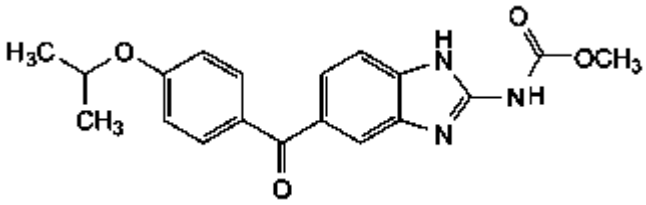
E. methyl [5-(2-fluorobenzoyl)-1*H*-benzimidazol-2-yl]carbamate,



F. methyl [5-(4-fluorobenzoyl)-1-methyl-1*H*-benzimidazol-2-yl]carbamate,

www.webofpharma.com

https://thuocngocanh.com/



G. methyl [5-[4-(1-methylethoxy)benzoyl]-1*H*-benzimidazol-2-yl]carbamate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flucloxacillin Capsules

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Flucloxacillin Capsules contain Flucloxacillin Sodium.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of flucloxacillin, $C_{19}H_{17}ClFN_3O_5S$

92.5 to 110.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum* of the contents of the capsules, Appendix II A, is concordant with the *reference spectrum* of flucloxacillin sodium *(RS 145)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the contents of the capsules containing the equivalent of 0.1 g of flucloxacillin with 80 mL of the mobile phase for 15 minutes, add sufficient of the mobile phase to produce 100 mL and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Solution (3) contains 0.01% w/v of each of *flucloxacillin sodium BPCRS* and *cloxacillin sodium BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a mixture of 25 volumes of *acetonitrile* and 75 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide* and (c) a detection wavelength of 225 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to cloxacillin and flucloxacillin is at least 2.5.

For solution (1) allow the chromatography to proceed for six times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%) and the sum of the areas of any such peaks is not greater than 5 times the area of the principal peak in the chromatogram

www.webofpharma.com

https://thuocngocanh.com/

obtained with solution (2) (5%). Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) shake a quantity of the mixed contents of 20 capsules containing the equivalent of 50 mg of flucloxacillin with 40 mL of the mobile phase for 15 minutes, add sufficient of the mobile phase to produce 50 mL, filter and dilute 5 volumes of the resulting solution to 50 volumes with the mobile phase. Solution (2) contains 0.011% w/v of *flucloxacillin sodium BPCRS* in the mobile phase. Solution (3) contains 0.01% w/v of each of *flucloxacillin sodium BPCRS* and *cloxacillin sodium BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a mixture of 25 volumes of *acetonitrile* and 75 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide* and (c) a detection wavelength of 225 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the first peak (cloxacillin) and the second peak (flucloxacillin) is at least 2.5.

Calculate the content of $C_{19}H_{17}ClFN_3O_5S$ in the capsules using the declared content of $C_{19}H_{16}ClFN_3NaO_5S$ in *flucloxacillin sodium BPCRS*. Each mg of $C_{19}H_{16}ClFN_3NaO_5S$ is equivalent to 0.9538 mg of $C_{19}H_{17}ClFN_3O_5S$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of flucloxacillin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flucloxacillin Infusion

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Penicillin antibacterial.

DEFINITION

Flucloxacillin Infusion is a sterile solution containing Flucloxacillin Sodium Monohydrate and a suitable buffer. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the infusion also complies with the requirements stated under Unlicensed Medicines.

Content of flucloxacillin, $C_{19}H_{17}ClFN_3O_5S$

90.0 to 105.0% of the stated amount.

CHARACTERS

A clear, colourless solution.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the infusion with sufficient *phosphate buffer pH 7.0* to produce a solution containing the equivalent of 0.25% w/v of flucloxacillin.

(2) 0.25% w/v of *flucloxacillin sodium BPCRS* in *phosphate buffer pH 7.0*.

(3) 0.25% w/v of each of *cloxacillin sodium BPCRS*, *dicloxacillin sodium BPCRS* and *flucloxacillin sodium BPCRS* in *phosphate buffer pH 7.0*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel silanised plate* (Merck silanised silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 1 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, expose to iodine vapour until the spots appear and examine in daylight.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

30 volumes of *acetone* and 70 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid* .

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 5.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the infusion with sufficient of the mobile phase to produce a solution containing the equivalent of 0.1% w/v of flucloxacillin.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(3) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.
(4) 0.01% w/v of each of *cloxacillin sodium BPCRS* and *flucloxacillin sodium BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for six times the retention time of the principal peak.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of flucloxacillin is about 12 minutes and the relative retention of cloxacillin is about 0.8.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to cloxacillin and flucloxacillin is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

Bacterial endotoxins

Dilute the infusion with *water BET* to contain the equivalent of 9 mg of flucloxacillin per mL (solution A). The endotoxin limit concentration of solution A is 3.5 IU per mL, Appendix XIV C.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a volume of the infusion with sufficient of the mobile phase to produce a solution containing the equivalent of 0.1% w/v of flucloxacillin; dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(2) 0.011% w/v of *flucloxacillin sodium BPCRS* in the mobile phase.
(3) 0.01% w/v of each of *cloxacillin sodium BPCRS* and *flucloxacillin sodium BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to cloxacillin and flucloxacillin is at least 2.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{17}ClFN_3O_5S$ in the infusion using the declared content of $C_{19}H_{16}ClFN_3NaO_5S$ in *flucloxacillin sodium BPCRS*.

Each mg of $C_{19}H_{16}ClFN_3NaO_5S$ is equivalent to 0.9538 mg of $C_{19}H_{17}ClFN_3O_5S$.

STORAGE

Flucloxacillin Infusion should be stored at a temperature of 2° to 8°.

LABELLING

www.webofpharma.com

https://thuocngocanh.com/

The quantity of active ingredient is stated in terms of the equivalent amount of flucloxacillin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flucloxacillin Injection

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Flucloxacillin Injection is a sterile solution of Flucloxacillin Sodium in Water for Injections. It is prepared by dissolving Flucloxacillin Sodium for Injection in the requisite amount of Water for Injections before use.

The injection complies with the requirements stated under Parenteral Preparations.

STORAGE

Flucloxacillin Injection should be used immediately after preparation but, in any case, within the period recommended by the manufacturer when prepared and stored strictly in accordance with the manufacturer's instructions.

FLUCLOXACILLIN SODIUM FOR INJECTION

DEFINITION

Flucloxacillin Sodium for Injection is a sterile material consisting of Flucloxacillin Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of flucloxacillin, $C_{19}H_{17}ClFN_3O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of flucloxacillin sodium *(RS 145)*.

B. Yield reaction B characteristic of *sodium salts*, Appendix VI.

TESTS

Acidity or alkalinity

www.webofpharma.com

https://thuocngocanh.com/

pH of a solution containing the equivalent of 10% w/v of flucloxacillin, 5.0 to 7.0, Appendix V L.

Related substances

Comply with the test described under Flucloxacillin Capsules but using a solution prepared in the following manner as solution (1). Shake a quantity of the contents of the sealed container containing the equivalent of 0.1 g of flucloxacillin with 80 mL of the mobile phase for 15 minutes, add sufficient of the mobile phase to produce 100 mL and filter.

Water

Not more than 4.5% w/w, Appendix IX C. Use 0.3 g.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the contents of the sealed container in *water BET* to give a solution containing the equivalent of 9 mg of flucloxacillin per mL (solution A). The endotoxin limit concentration of solution A is 3.5 IU per mL.

ASSAY

Determine the weight of the contents of 10 containers as described in the test for *uniformity of weight*, Appendix XII C1, Powders for Parenteral Administration.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dissolve a quantity of the mixed contents of 10 containers containing the equivalent of 50 mg of flucloxacillin in sufficient of the mobile phase to produce 50 mL and dilute 5 volumes of the resulting solution to 50 volumes with the mobile phase. Solution (2) contains 0.011% w/v of *flucloxacillin sodium BPCRS* in the mobile phase. Solution (3) contains 0.01% w/v of each of *flucloxacillin sodium BPCRS* and *cloxacillin sodium BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a mixture of 25 volumes of *acetonitrile* and 75 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide* and (c) a detection wavelength of 225 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the first peak (cloxacillin) and the second peak (flucloxacillin) is at least 2.5.

Calculate the content of $C_{19}H_{17}ClFN_3O_5S$ in a container of average content weight using the declared content of $C_{19}H_{16}ClFN_3NaO_5S$ in *flucloxacillin sodium BPCRS*. Each mg of $C_{19}H_{16}ClFN_3NaO_5S$ is equivalent to 0.9538 mg of $C_{19}H_{17}ClFN_3O_5S$.

LABELLING

The label of the sealed container states the quantity of Flucloxacillin Sodium contained in it in terms of the equivalent amount of flucloxacillin.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

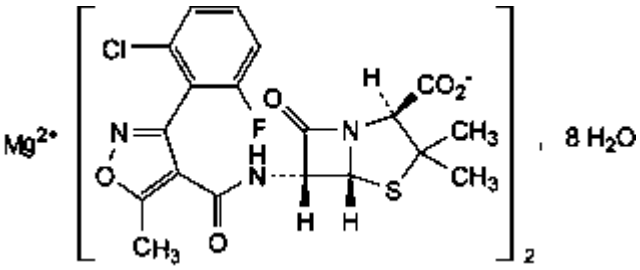
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flucloxacillin Magnesium Octahydrate

General Notices

Flucloxacillin Magnesium

(Ph. Eur. monograph 2346)



$C_{38}H_{32}Cl_2F_2MgN_6O_{10}S_2,8H_2O$ 1074 *58486-36-5*

Action and use

Penicillin antibacterial.

Preparations

Flucloxacillin Oral Suspension

Co-fluampicil Oral Suspension

Ph Eur

DEFINITION

Magnesium bis[(2*S*,5*R*,6*R*)-6-[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] octahydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in methanol.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flucloxacillin magnesium octahydrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *water R*.

Reference solution (a) Dissolve 25 mg of *flucloxacillin sodium CRS* in 5 mL of *water R*.

Reference solution (b) Dissolve 25 mg of *cloxacillin sodium CRS*, 25 mg of *dicloxacillin sodium CRS* and 25 mg of *flucloxacillin sodium CRS* in 5 mL of *water R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose the plate to iodine vapour until the spots appear.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. It gives the reaction of magnesium (2.3.1).

TESTS

pH (2.2.3)

www.webofpharma.com

https://thuocngocanh.com/

4.5 to 6.5.

Dissolve 0.25 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 163 to + 175 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *flucloxacillin sodium CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of test solution (b) to 50.0 mL with the mobile phase.

Reference solution (c) In order to prepare impurity A *in situ*, add 1 mL of *sodium carbonate solution R* to 10 mg of the substance to be examined, dilute to 25 mL with *water R* and place in an oven at 70 °C for 20 min.

Reference solution (d) Dilute 1 mL of reference solution (c) to 10 mL with a 27 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 3.5 with *dilute phosphoric acid R*.

Reference solution (e) In order to prepare impurity B *in situ*, add 5 mL of *dilute hydrochloric acid R* to 10 mL of reference solution (c), dilute to 25 mL with *water R* and place in an oven at 70 °C for 1 h. Dilute 1 mL of this solution to 5 mL with a 27 g/L solution of *dipotassium hydrogen phosphate R* previously adjusted to pH 7.0 with *phosphoric acid R*.

Reference solution (f) Dilute 2 mL of reference solution (a) to 10 mL with reference solution (e).

Reference solution (g) Dissolve 1.5 mg of *flucloxacillin impurity C CRS* in 1 mL of the mobile phase and dilute to 50 mL with the mobile phase.

Reference solution (h) Dissolve 1 mg of *flucloxacillin impurity D CRS* in 100 mL of the mobile phase.

Reference solution (i) Dissolve 1 mg of *flucloxacillin impurity E CRS* in 100 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 25 volumes of *acetonitrile R1* and 75 volumes of a 2.7 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with *dilute sodium hydroxide solution R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (d), (e), (f), (g), (h) and (i).

Run time 7 times the retention time of flucloxacillin.

Identification of impurities Use the chromatograms obtained with reference solutions (d), (e), (g), (h) and (i) to identify the peaks due to impurities A, B, C, D and E respectively.

Relative retention With reference to flucloxacillin (retention time = about 8 min): impurity C = about 0.2; impurity A (isomer 1) = about 0.3; impurity A (isomer 2) = about 0.5; impurity D = about 0.6; impurity B (isomer 1) = about 0.8; impurity B (isomer 2) = about 0.9; impurity E = about 6.

System suitability Reference solution (f):

— *resolution*: minimum 2.0 between the 2nd peak due to impurity B (isomer 2) and the peak due to flucloxacillin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 3.3;

— *impurity A* (sum of the 2 isomers): the sum of the areas of the 2 peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *impurity B* (sum of the 2 isomers): the sum of the areas of the 2 peaks is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurities D, E*: for each impurity, not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *any other impurity*: for each impurity, not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

2-Ethylhexanoic acid (*2.4.28*)

Maximum 0.8 per cent *m/m*.

www.webofpharma.com

https://thuvienthuocngocanh.com/

Water (*2.5.12*)

12.0 per cent to 15.0 per cent, determined on 0.100 g.

ASSAY

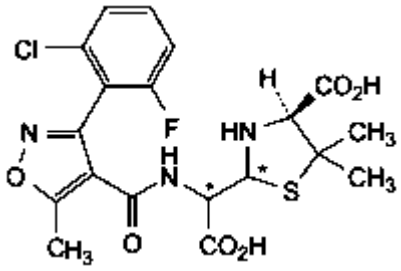
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (a).

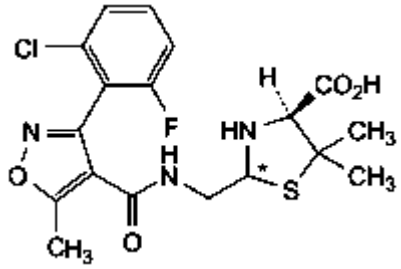
Calculate the percentage content of $C_{38}H_{32}Cl_2F_2MgN_6O_{10}S_2$ from the declared content of *flucloxacillin sodium CRS*, multiplying by 0.9773.

IMPURITIES

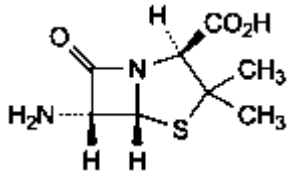
Specified impurities *A, B, C, D, E.*



A. (4*S*)-2-[carboxy[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of flucloxacillin),



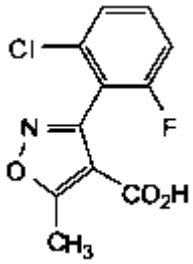
B. (2*RS*,4*S*)-2-[[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of flucloxacillin),



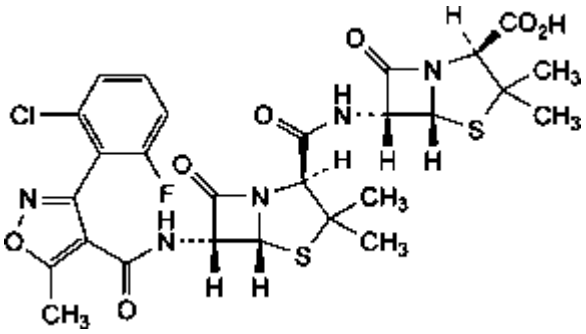
C. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),

www.webofpharma.com

https://thuocngocanh.com/



D. 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylic acid,



E. (2*S*,5*R*,6*R*)-6-[[[(2*S*,5*R*,6*R*)-6-[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-APA flucloxacillin amide).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flucloxacillin Oral Solution

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Flucloxacillin Oral Solution is a solution of Flucloxacillin Sodium in a suitable flavoured vehicle. It is prepared by dissolving the dry ingredients in the specified volume of water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

For the following tests prepare the oral solution as directed on the label. The solution, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of flucloxacillin, $C_{19}H_{17}ClFN_3O_5S$

When freshly constituted, not more than 120.0% of the stated amount. When stored at the temperature and for the period stated on the label during which the oral solution may be expected to be satisfactory for use, not less than 80.0% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel silanised plate* (Merck silanised silica gel 60 plates are suitable) and a mixture of 30 volumes of *acetone* and 70 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid* as the mobile phase. Apply separately to the plate 1 µL of each of the following solutions. For solution (1) dilute a quantity of the oral solution containing the equivalent of 50 mg of flucloxacillin to 20 mL with *phosphate buffer pH 7.0*. Solution (2) contains 0.25% w/v of *flucloxacillin sodium BPCRS* in *phosphate buffer pH 7.0*. Solution (3) contains 0.25% w/v of each of *cloxacillin sodium BPCRS*, *dicloxacillin sodium BPCRS* and *flucloxacillin sodium BPCRS* in *phosphate buffer pH 7.0*. After removal of the plate, allow it to dry in air, expose to iodine vapour until the spots appear and examine in daylight. The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

TESTS

Acidity or alkalinity

pH, 4.0 to 7.0, Appendix V L.

ASSAY

https://thietbiuocngocanh.com/

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute a weighed quantity of the oral solution containing the equivalent of 50 mg of flucloxacillin to 50 mL with the mobile phase and dilute 5 volumes of this solution to 50 volumes with the mobile phase. Solution (2) contains 0.011% w/v of *flucloxacillin sodium BPCRS* in the mobile phase. Solution (3) contains 0.01% w/v of each of *flucloxacillin sodium BPCRS* and *cloxacillin sodium BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a mixture of 25 volumes of *acetonitrile* and 75 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide* and (c) a detection wavelength of 225 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the first peak (cloxacillin) and the second peak (flucloxacillin) is at least 2.5.

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{19}H_{17}ClFN_3O_5S$, weight in volume, using the declared content of $C_{19}H_{16}ClFN_3NaO_5S$ in *flucloxacillin sodium BPCRS*. Each mg of $C_{19}H_{16}ClFN_3NaO_5S$ is equivalent to 0.9538 mg of $C_{19}H_{17}ClFN_3O_5S$.

Repeat the procedure using a portion of the oral solution that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The oral solution should be stored at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of flucloxacillin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flucloxacillin Oral Suspension

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Flucloxacillin Oral Suspension is a suspension of Flucloxacillin Magnesium Octahydrate in a suitable flavoured vehicle. It is prepared by dispersing the dry ingredients in the specified volume of water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

For the following tests prepare the oral suspension as directed on the label. The suspension examined immediately after preparation, unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of flucloxacillin, $C_{19}H_{17}ClFN_3O_5S$

When freshly constituted, not more than 120.0% of the stated amount. When stored at the temperature and for the period stated on the label during which the oral suspension may be expected to be satisfactory for use, not less than 80.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel silanised plate* (Merck silanised silica gel 60 plates are suitable) and a mixture of 30 volumes of *acetone* and 70 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid* as the mobile phase. Apply separately to the plate 1 µL of each of the following solutions. For solution (1) dilute a quantity of the oral suspension containing the equivalent of 50 mg of flucloxacillin to 20 mL with *phosphate buffer pH 7.0*. Solution (2) contains 0.25% w/v of *flucloxacillin sodium BPCRS* in *phosphate buffer pH 7.0*. Solution (3) contains 0.25% w/v of each of *cloxacillin sodium BPCRS*, *dicloxacillin sodium BPCRS* and *flucloxacillin sodium BPCRS* in *phosphate buffer pH 7.0*. After removal of the plate, allow it to dry in air, expose to iodine vapour until the spots appear and examine in daylight. The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2). The test is not valid unless the chromatogram obtained with solution (3) shows three clearly separated spots.

B. Dilute a quantity of the oral suspension containing the equivalent of 50 mg of flucloxacillin to 20 mL with *water*, shake to dissolve and filter if necessary. The filtrate yields reaction B characteristic of *magnesium salts*, Appendix VI.

TESTS

Acidity

www.webofpharma.com

https://thietbiuocngocanh.com/

pH, 4.8 to 5.8, Appendix V L.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute a weighed quantity of the oral suspension containing the equivalent of 50 mg of flucloxacillin to 50 mL with the mobile phase and dilute 5 volumes of the solution to 50 volumes with the mobile phase. Solution (2) contains 0.011% w/v of *flucloxacillin sodium BPCRS* in the mobile phase. Solution (3) contains 0.01% w/v of each of *flucloxacillin sodium BPCRS* and *cloxacillin sodium BPCRS* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil 5 ODS is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a mixture of 25 volumes of *acetonitrile* and 75 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 5.0 with 2M *sodium hydroxide* and (c) a detection wavelength of 225 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the first peak (cloxacillin) and the second peak (flucloxacillin) is at least 2.5.

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{19}H_{17}ClFN_3O_5S$, weight in volume, using the declared content of $C_{19}H_{16}ClFN_3NaO_5S$ in *flucloxacillin sodium BPCRS*. Each mg of $C_{19}H_{16}ClFN_3NaO_5S$ is equivalent to 0.9538 mg of $C_{19}H_{17}ClFN_3O_5S$.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The oral suspension should be stored at the temperature and used within the period stated on the label.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of flucloxacillin.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

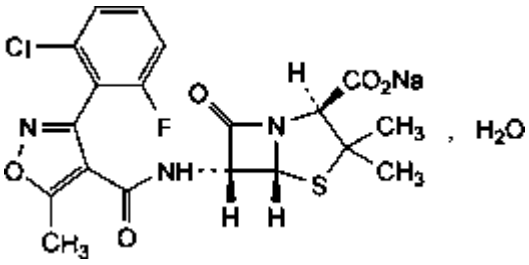
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flucloxacillin Sodium Monohydrate

General Notices

Flucloxacillin Sodium

(Ph. Eur. monograph 0668)



$C_{19}H_{16}ClFN_3NaO_5S,H_2O$ 493.9 *34214-51-2*

Action and use

Penicillin antibacterial.

Preparations

Flucloxacillin Capsules

Co-fluampicil Capsules

Flucloxacillin Infusion

Flucloxacillin Injection

Flucloxacillin Oral Solution

Ph Eur

DEFINITION

Sodium (2*S*,5*R*,6*R*)-6-[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.

Semi-synthetic product derived from a fermentation product.

Content

95.0 per cent to 102.0 per cent (anhydrous substance).

www.webofpharma.com

https://thuocngocanh.com/

PRODUCTION

The manufacturing process is evaluated to determine the potential presence of *N*,*N*-dimethylaniline. Where necessary, the manufacturing process is validated to demonstrate that the flucloxacillin sodium monohydrate complies with the following test:

_N_,_N_-Dimethylaniline (2.4.26, Method B)

Maximum 20 ppm.

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Freely soluble in water and in methanol, soluble in ethanol (96 per cent), practically insoluble in dichloromethane.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flucloxacillin sodium CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in 5 mL of *water R*.

Reference solution (a) Dissolve 25 mg of *flucloxacillin sodium CRS* in 5 mL of *water R*.

Reference solution (b) Dissolve 25 mg of *cloxacillin sodium CRS*, 25 mg of *dicloxacillin sodium CRS* and 25 mg of *flucloxacillin sodium CRS* in 5 mL of *water R*.

Plate *TLC silanised silica gel plate R*.

Mobile phase Mix 30 volumes of *acetone R* and 70 volumes of a 154 g/L solution of *ammonium acetate R* adjusted to pH 5.0 with *glacial acetic acid R*.

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

www.webofpharma.com

https://thuocngocanh.com/

Detection Expose to iodine vapour until the spots appear and examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 mL of *water R* and add 2 mL of *sulfuric acid-formaldehyde reagent R*. Mix the contents of the tube by swirling; the colour of the solution is slightly greenish-yellow. Place the test-tube in a water-bath for 1 min; the solution becomes yellow.

D. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 430 nm is not greater than 0.04.

pH (*2.2.3*)

5.0 to 7.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *water R*, *acetonitrile R* (50:50 *V/V*).

Test solution (a) Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Protect the solution from light.

Test solution (b) Dilute 2.0 mL of test solution (a) to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of *flucloxacillin sodium CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Protect the solution from light.

Reference solution (b) Dilute 2.0 mL of reference solution (a) to 20.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of *flucloxacillin for peak identification CRS* (containing impurities A, B, C, D, E, F, G, H, I, J and K) in the solvent mixture and dilute to 5 mL with the solvent mixture. Protect the solution from light.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (e) Dissolve 5 mg of *flucloxacillin impurity D CRS* in the solvent mixture and dilute to 50 mL with the solvent mixture. Protect the solution from light.

Reference solution (f) Dissolve 20 mg of *flucloxacillin sodium CRS* in the solvent mixture, add 2 mL of reference solution (e) and dilute to 20 mL with the solvent mixture. Protect the solution from light.

Reference solution (g) Dilute 2 mL of reference solution (f) to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.18 g of *sodium hexanesulfonate monohydrate for ion-pair chromatography R* in *water for chromatography R*, add 0.8 mL of *concentrated ammonia R1* and dilute to 1000 mL with *water for chromatography R*; adjust to pH 2.8-3.0 with concentrated *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	80 → 45	20 → 55
30 - 35	45 → 35	55 → 65

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL of test solution (a) and reference solutions (c), (d) and (f).

Identification of impurities Use the chromatogram supplied with *flucloxacillin for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, E, F, G, H, I, J and K.

Relative retention With reference to flucloxacillin (retention time = about 19 min): impurity C = about 0.09; impurity A (isomer 1) = about 0.48; impurity A (isomer 2) = about 0.50; impurity F = about 0.55; impurity G = about 0.65; impurity B (isomer 1) = about 0.76; impurity B (isomer 2) = about 0.79; impurity D = about 0.94; impurity H = about 1.22; impurity E = about 1.26; impurity I = about 1.35; impurity J = about 1.57; impurity K = about 1.59.

System suitability Reference solution (f):

— *resolution*: minimum 1.5 between the peaks due to impurity D and flucloxacillin.

www.webofpharma.com

https://thuocngocanh.com/

Calculation of percentage contents:

— for each impurity, use the concentration of flucloxacillin sodium monohydrate in reference solution (c);

— *correction factor*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.3; impurity C = 4.2.

Limits:

— *impurity A (sum of the 2 isomers)*: maximum 2.0 per cent;

— *impurity B (sum of the 2 isomers)*: maximum 1.5 per cent;

— *impurities C, E*: for each impurity, maximum 1.0 per cent;

— *impurity H*: maximum 0.5 per cent;

— *impurities F, I, J, K*: for each impurity, maximum 0.4 per cent;

— *impurities D, G*: for each impurity, maximum 0.3 per cent;

— *any other impurity*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 5.0 per cent;

— *reporting threshold*: 0.05 per cent.

2-Ethylhexanoic acid (2.4.28)

Maximum 0.8 per cent *m/m*.

Water (2.5.12)

3.0 per cent to 4.5 per cent, determined on 0.300 g.

Pyrogens (2.6.8)

If intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of pyrogens, it complies with the test. Inject per kilogram of the rabbit's mass 1 mL of a solution in *water for injections R* containing 20 mg of the substance to be examined per millilitre.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase:

— *mobile phase A*: dissolve 1.18 g of *sodium hexanesulfonate monohydrate for ion-pair chromatography R* in *water for chromatography R*, add 0.8 mL of *concentrated ammonia R1* and dilute to 1000 mL with *water for chromatography R*; adjust to pH 3.0-3.2 with concentrated *phosphoric acid R*;

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	65 → 41	35 → 59

Flow rate 1.8 mL/min.

Injection Test solution (b) and reference solutions (b) and (g).

Relative retention With reference to flucloxacillin (retention time = about 5.3 min): impurity D = about 1.04.

System suitability Reference solution (g):

— *resolution*: minimum 1.5 between the peaks due to impurity D and flucloxacillin.

Calculate the percentage content of $C_{19}H_{16}ClFN_3NaO_5S$ using the chromatogram obtained with reference solution (b) and taking into account the assigned content of *flucloxacillin sodium CRS*.

STORAGE

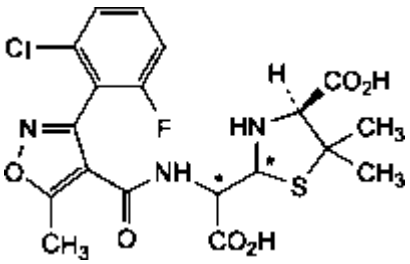
In an airtight container, at a temperature not exceeding 25 °C. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

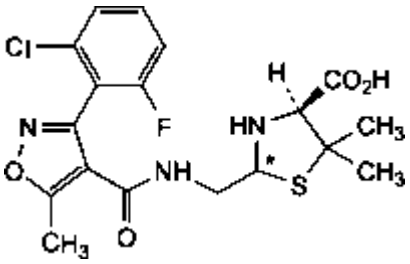
Specified impurities *A, B, C, D, E, F, G, H, I, J, K.*



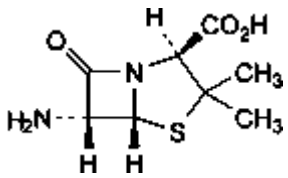
A. (2Ξ,4*S*)-2-[(Ξ)-carboxy[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penicilloic acids of flucloxacillin),

www.webofpharma.com

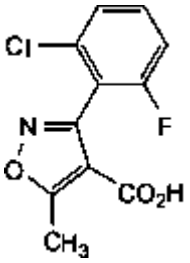
https://thuocngocanh.com/



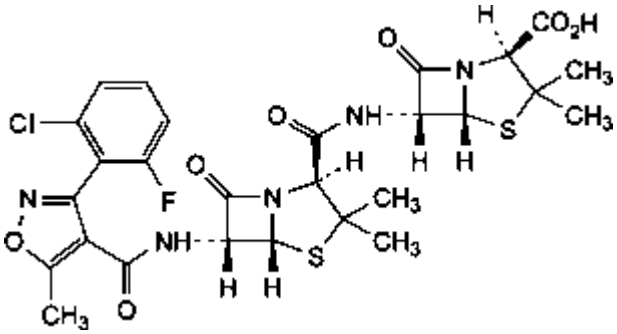
B. (2Ξ,4*S*)-2-[[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (penilloic acids of flucloxacillin),



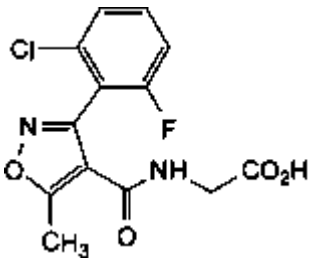
C. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



D. 3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazole-4-carboxylic acid,



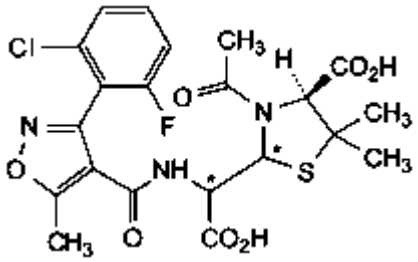
E. (2*S*,5*R*,6*R*)-6-[(2*S*,5*R*,6*R*)-6-[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-amido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-APA flucloxacillin amide),



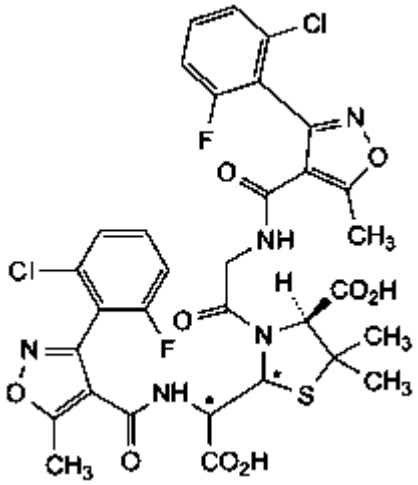
F. [3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]acetic acid,

www.webofpharma.com

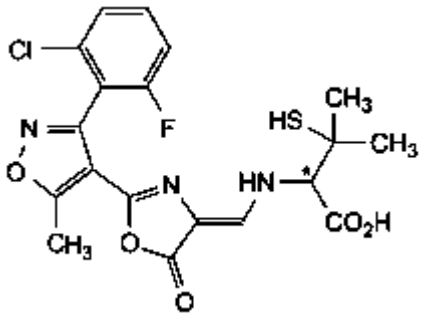
https://thuocngocanh.com/



G. (2Ξ,4*S*)-3-acetyl-2-[(Ξ)-carboxy[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]methyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid,



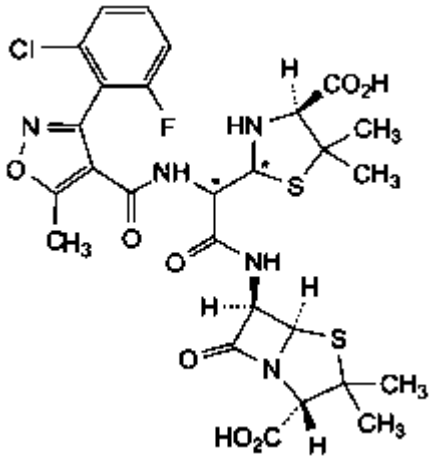
H. (2Ξ,4*S*)-2-[(Ξ)-carboxy[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]methyl]-3-[[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]acetyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid,



I. (2Ξ)-2-[[(*Z*)-[2-[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-yl]-5-oxo-1,3-oxazol-4(5*H*)-ylidene]methyl]amino]-3-methyl-3-sulfanylbutanoic acid,

www.webofpharma.com

https://thuocngocanh.com/



J. (2*S*,5*R*,6*R*)-6-[(2Ξ)-2-[(2Ξ,4*S*)-4-carboxy-5,5-dimethyl-1,3-thiazolidin-2-yl]-2-[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazol-4-amido]acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,

K. unknown structure.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

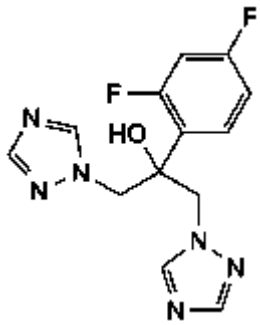
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluconazole

General Notices

(Ph. Eur. monograph 2287)



$C_{13}H_{12}F_2N_6O$ 306.3 *86386-73-4*

Action and use

Antifungal.

Preparations

Fluconazole Capsules

Fluconazole Oral Suspension

Fluconazole Infusion

Ph Eur

DEFINITION

2-(2,4-Difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Slightly soluble in water, freely soluble in methanol, soluble in acetone.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *fluconazole CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methylene chloride R*, evaporate to dryness on a water-bath and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 1.0 g in *methanol R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase, sonicate if necessary, and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *fluconazole for peak identification CRS* (containing impurity A) in the mobile phase, sonicate if necessary, and dilute to 10 mL with the mobile phase.

Reference solution (c) Dissolve 3.0 mg of *fluconazole impurity B CRS* in the mobile phase, sonicate if necessary, and dilute to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve 3.0 mg of *fluconazole impurity C CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (e) To 1.0 mL of reference solution (d) add 1.0 mL of the test solution and dilute to 10.0 mL with the mobile phase.

Reference solution (f) Dilute 1.0 mL of reference solution (d) to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R1* (5 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 40 °C.

Mobile phase *acetonitrile R*, 0.63 g/L solution of *ammonium formate R* (14:86 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL of the test solution and reference solutions (a), (b), (c), (e) and (f).

Run time 3.5 times the retention time of fluconazole.

Identification of impurities Use the chromatogram supplied with *fluconazole for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B and the chromatogram obtained with reference solution (f) to identify the peak due to impurity C.

Relative retention With reference to fluconazole (retention time = about 11 min): impurity B = about 0.4; impurity A = about 0.5; impurity C = about 0.8.

System suitability Reference solution (e):

— *resolution*: minimum 3.0 between the peaks due to impurity C and fluconazole.

Limits:

— *impurity A*: not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (f) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: maximum 0.6 per cent;

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.125 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 15.32 mg of $C_{13}H_{12}F_2N_6O$.

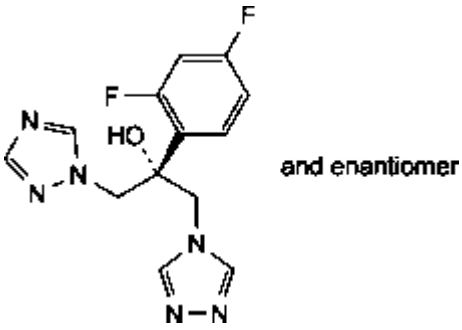
STORAGE

In an airtight container.

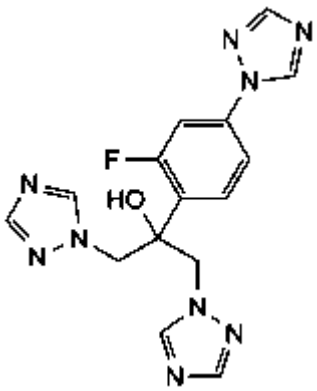
IMPURITIES

Specified impurities A, B, C.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) D, E, F, G, H, I.



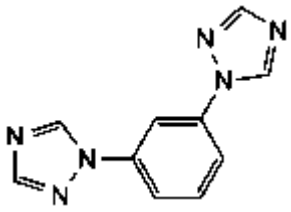
A. (2*RS*)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(4*H*-1,2,4-triazol-4-yl)propan-2-ol,



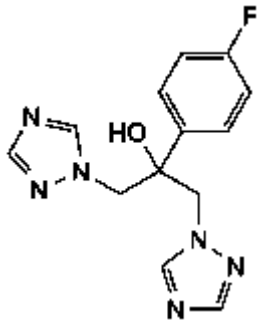
B. 2-[2-fluoro-4-(1*H*-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol,

www.webofpharma.com

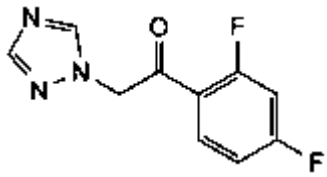
https://thuocngocanh.com/



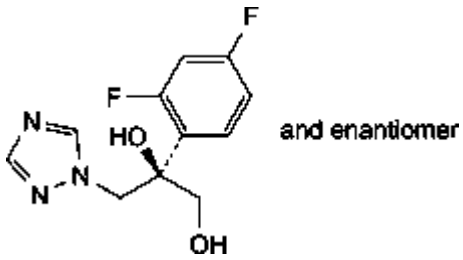
C. 1,1′-(1,3-phenylene)di-1*H*-1,2,4-triazole,



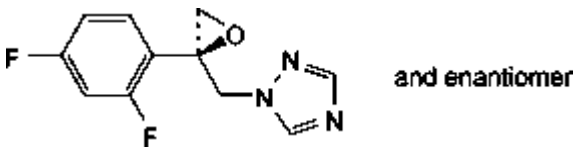
D. 2-(4-fluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol,



E. 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone,



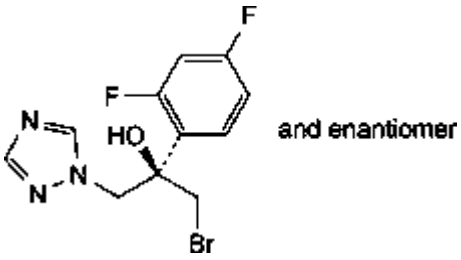
F. (2*RS*)-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propane-1,2-diol,



G. 1-[[(2*RS*)-2-(2,4-difluorophenyl)oxiran-2-yl]methyl]-1*H*-1,2,4-triazole,

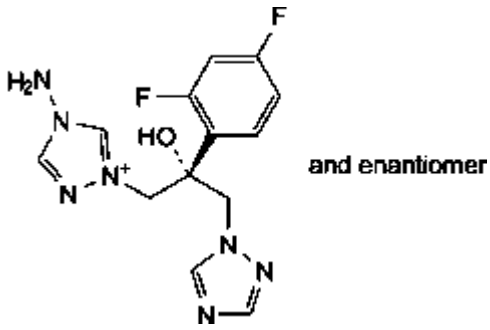
www.webofpharma.com

https://thuocngocanh.com/



and enantiomer

H. (2*RS*)-1-bromo-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol,



and enantiomer

I. 4-amino-1-[(2*RS*)-2-(2,4-difluorophenyl)-2-hydroxy-3(1*H*-1,2,4-triazol-1-yl)propyl]-4*H*-1,2,4-triazolium.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluconazole Capsules

General Notices

Action and use

Antifungal.

DEFINITION

Fluconazole Capsules contain Fluconazole.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of fluconazole, $C_{13}H_{12}F_2N_6O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered capsule contents containing 100 mg of Fluconazole with 10 mL of *methanol*. Filter and use the filtrate.

(2) 1.0% w/v of *fluconazole BPCRS* in *methanol*.

(3) 0.2% w/v of *fluconazole BPCRS* and 0.1% w/v of *ketoconazole BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 20 volumes of *methanol* and 80 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, and rotate the basket at 100 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, diluted with the dissolution medium, if necessary, to produce a solution containing 0.0056% w/v of Fluconazole, at 261 nm, Appendix II B using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0056% w/v solution of *fluconazole BPCRS* in dissolution medium at 261 nm using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of fluconazole, $C_{13}H_{12}F_2N_6O$, in the medium from the absorbances obtained and using the declared content of $C_{13}H_{12}F_2N_6O$ in *fluconazole BPCRS*.

LIMITS

The amount of fluconazole released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) To a quantity of powdered capsule contents containing 0.5 g of Fluconazole, add 25 mL and mix with the aid of ultrasound. Dilute to produce 50 mL, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume to 10 volumes.

(3) 0.1% w/v of *fluconazole impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 260 nm.

(f) Inject 20 µL of each solution.

www.webofpharma.com

https://thietbiuocngocanh.com/

(g) Allow the chromatography to proceed for 3.5 times the retention time of fluconazole.

MOBILE PHASE

14 volumes of *acetonitrile* and 86 volumes of 0.01M *ammonium formate*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to fluconazole (retention time about 11 minutes) are: impurity B, about 0.4; impurity A, about 0.5 and impurity C, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and fluconazole is at least 3.0.

LIMITS

Identify any peaks corresponding to impurities B and C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by correction factors of 0.15 and 0.05, respectively.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak due to impurity B is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the total content of impurities is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder the content of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) To a quantity of powdered capsule contents containing 0.5 g of Fluconazole add 50 mL, mix with the aid of ultrasound and dilute to produce 100 mL. Dilute 1 volume to 10 volumes, filter and use the filtrate.
(2) 0.05% w/v of *fluconazole BPCRS*.
(3) 0.1% w/v of *fluconazole impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and fluconazole is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{12}F_2N_6O$ in the capsules using the declared content of $C_{13}H_{12}F_2N_6O$ in *fluconazole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Fluconazole.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluconazole Oral Suspension

General Notices

Action and use

Antifungal.

DEFINITION

Fluconazole Oral Suspension is a suspension of Fluconazole in a suitable vehicle. It is prepared by dispersing the dry ingredients in the specified volume of Water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Suspensions stated under Oral Liquids.

For the following tests prepare the Oral Suspension as directed on the label. The suspension, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of fluconazole, $C_{13}H_{12}F_2N_6O$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the oral suspension containing 10 mg of Fluconazole with 3 mL of *methanol*. Add sufficient *methanol* to produce 5 mL, filter and use the filtrate.

(2) 0.2% w/v of *fluconazole BPCRS* in *methanol*.

(3) 0.2% w/v of *fluconazole BPCRS* and 0.1% w/v of *ketoconazole BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 20 volumes of *methanol* and 80 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

www.webofpharma.com

https://thuocngocanh.com/

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.0 to 5.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) To a quantity of the oral suspension containing 0.1 g of Fluconazole, add 25 mL and mix with the aid of ultrasound. Dilute to produce 50 mL, filter and use the filtrate.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.1% w/v of *fluconazole impurity standard BPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 260 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3.5 times the retention time of fluconazole.

MOBILE PHASE

14 volumes of *acetonitrile* and 86 volumes of 0.01M *ammonium formate*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to fluconazole (retention time about 11 minutes) are: impurity B, about 0.4; impurity A, about 0.5 and impurity C, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and fluconazole is at least 3.0.

LIMITS

Identify any peaks corresponding to impurities B and C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by correction factors of 0.15 and 0.05, respectively.

www.webofpharma.com

https://thietbiuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak due to impurity B is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the total content of impurities is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) To a weighed quantity of the oral suspension containing 25 mg, add 20 mL and shake. Dilute to 50 mL, filter and use the filtrate.
(2) 0.05% w/v of *fluconazole BPCRS*.
(3) 0.1% w/v of *fluconazole impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and fluconazole is at least 3.0.

DETERMINATION OF CONTENT

Determine the weight per mL of the oral suspension, Appendix V G, and calculate the content of $C_{13}H_{12}F_2N_6O$, weight in volume, using the declared content of $C_{13}H_{12}F_2N_6O$ in *fluconazole BPCRS*.

Repeat the procedure using a portion of the oral suspension that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

IMPURITIES

The impurities limited by the requirements of this monograph include A, B and C listed under Fluconazole.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

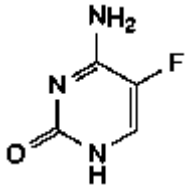
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flucytosine

General Notices

(Ph. Eur. monograph 0766)



$C_4H_4FN_3O$ 129.1 *2022-85-7*

Action and use

Antifungal.

Ph Eur

DEFINITION

4-Amino-5-fluoropyrimidin-2(1*H*)-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *flucytosine CRS*.

B. Thin-layer chromatography (*2.2.27*).

Solvent mixture *water R*, *methanol R* (10:15 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution Dissolve 10 mg of *flucytosine CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *anhydrous formic acid R*, *water R*, *methanol R*, *ethyl acetate R* (1:15:25:60 *V/V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate in an unsaturated tank with the mobile phase. Then allow the solvents to evaporate.

Detection At the bottom of a chromatography tank place an evaporating dish containing a mixture of 1 volume of *hydrochloric acid R1*, 1 volume of *water R* and 2 volumes of a 15 g/L solution of *potassium permanganate R*. Close the tank and allow to stand for 15 min. Place the dried plate in the tank and close the tank. Leave the plate in contact with the chlorine vapour for 5 min. Withdraw the plate and place it in a current of cold air until the excess of chlorine is removed and an area of the coating below the points of application does not give a blue colour with a drop of *potassium iodide and starch solution R*. Spray with *potassium iodide and starch solution R*. Examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter and add to the filtrate a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The colour of the solution changes from red to yellow.

D. To 5 mL of solution S (see Tests) add 0.15 mL of *bromine water R* and shake. The colour of the solution is discharged.

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 or Y_7 (*2.2.2, Method II*).

Related substances

Liquid chromatography (*2.2.29*).

www.webofpharma.com

https://thuocngocanh.com/

Solvent mixture Dissolve 13.6 g of *potassium dihydrogen phosphate R* in 950 mL of *water R*. Add 50 mL of *methanol R*. Mix thoroughly.

Test solution Dissolve 15.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Mix well. Sonicate for 5 min. Mix thoroughly. Sonicate the solution for 5 min. Mix thoroughly.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 15.0 mg of *fluorouracil CRS* (impurity A) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Mix well. Sonicate for 5 min. Mix thoroughly. Sonicate the solution for 5 min. Mix thoroughly. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of *flucytosine for system suitability CRS* (containing impurity B) in 0.5 mL of the solvent mixture and add 0.5 mL of reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 13.6 g of *potassium dihydrogen phosphate R* in 950 mL of *water R*. Filter through a membrane filter (nominal pore size 0.45 µm). Adjust to pH 2.0 by adding *phosphoric acid R* and add 50 mL of *methanol R*. Mix thoroughly.

Flow rate 1.1 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL of the test solution and reference solutions (a) and (c).

Run time 15 times the retention time of flucytosine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to flucytosine (retention time = about 2 min): impurity A = about 1.7; impurity B = about 13.3.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to flucytosine and impurity A in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 50 for the peak due to impurity B in the chromatogram obtained with reference solution (c);

— *symmetry factor*: maximum 2.0 for the peak due to flucytosine in the chromatogram obtained with reference solution (a).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.6;

www.webofpharma.com

https://thuocngocanh.com/

— *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *impurity B*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Fluorides

Maximum 200 ppm.

Potentiometry (*2.2.36, Method I*). *Prepare and store all solutions in plastic containers*.

Buffer solution Dissolve 58 g of *sodium chloride R* in 500 mL of *water R*. Add 57 mL of *glacial acetic acid R* and 200 mL of a 100 g/L solution of *cyclohexylenedinitrilotetra-acetic acid R* in *1 M sodium hydroxide*. Adjust the pH to 5.0-5.5 with a 200 g/L solution of *sodium hydroxide R* and dilute to 1000.0 mL with *water R*.

Test solution Dissolve 1.00 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solutions Dissolve 4.42 g of *sodium fluoride R*, previously dried at 120 °C for 2 h, in 300 mL of *water R* and dilute to 1000.0 mL with the same solvent (solution (a): 1.9 g/L of fluoride). Prepare 3 reference solutions by dilution of solution (a) 1 in 100, 1 in 1000 and 1 in 10 000 respectively.

Indicator electrode Fluoride selective.

Reference electrode Silver-silver chloride.

To 20.0 mL of the test solution and each reference solution, add 10.0 mL of the buffer solution and stir with a magnetic stirrer. Introduce the electrodes into the solution and allow to stand for 5 min with constant stirring.

Calculate the concentration of fluorides using the calibration curve.

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.100 g in 40 mL of *anhydrous acetic acid R* and add 100 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid* determining the end-point potentiometrically (*2.2.20*).

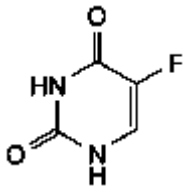
1 mL of *0.1 M perchloric acid* is equivalent to 12.91 mg of $C_4H_4FN_3O$.

STORAGE

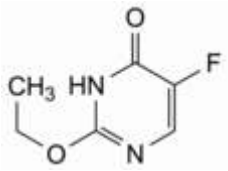
Protected from light.

IMPURITIES

Specified impurities *A, B.*



A. 5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (fluorouracil),



B. 2-ethoxy-5-fluoropyrimidin-4(3*H*)-one.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

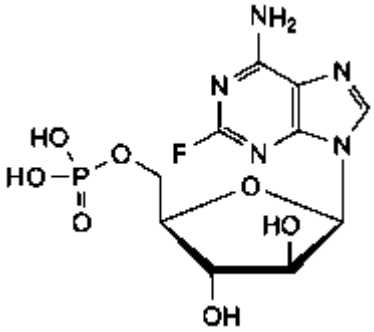
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fludarabine Phosphate

General Notices

(Ph. Eur. monograph 1781)



$C_{10}H_{13}FN_5O_7P$ 365.2 *75607-67-9*

Action and use

Purine analogue; cytotoxic.

Ph Eur

DEFINITION

2-Fluoro-9-(5-*O*-phosphono-β-D-arabinofuranosyl)-9*H*-purin-6-amine.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Slightly soluble in water, freely soluble in dimethylformamide, very slightly soluble in anhydrous ethanol.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *fludarabine phosphate CRS*.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Dissolve 50 mg in 5.0 mL of *dimethylformamide R* using sonication.

Specific optical rotation (*2.2.7*)

+ 10.0 to + 14.0 (anhydrous substance).

Dissolve 0.100 g in *water R* using sonication and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*): use the normalisation procedure. *Prepare the solutions immediately before use.*

Test solution (a) Dissolve 20 mg of the substance to be examined in 50 mL of *water R* using sonication and dilute to 100.0 mL with the same solvent.

Test solution (b) Dissolve 24.0 mg of the substance to be examined in 50 mL of *water R*; using sonication and dilute to 100.0 mL with the same solvent. Dilute 25.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (a) In order to prepare impurities A and B *in situ*, dissolve 20 mg of the substance to be examined in 20 mL of a 10.3 g/L solution of *hydrochloric acid R* using sonication. Heat in a water-bath at 80 °C for 15 min, cool to room temperature, mix and dilute to 100 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (c) Dissolve 5 mg of *fludarabine for system suitability CRS* (containing impurities D, E and F) in 10 mL of *water R* using sonication and dilute to 25 mL with the same solvent.

Reference solution (d) Dissolve 2 mg of *fludarabine for peak identification CRS* (containing impurity C) in 5 mL of *water R* using sonication and dilute to 10 mL with the same solvent.

Reference solution (e) Dissolve 24.0 mg of *fludarabine phosphate CRS* in 50 mL of *water R* using sonication and dilute to 100.0 mL with the same solvent. Dilute 25.0 mL of the solution to 100.0 mL with the mobile phase.

Blank solution 2.06 g/L solution of *hydrochloric acid R*.

A. Early eluting impurities.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Mix 60 volumes of *methanol R* and 940 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 260 nm and at 292 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (d).

Run time 4.5 times the retention time of the principal peak in the chromatogram obtained with test solution (a).

Identification of impurities Use the chromatogram obtained with reference solution (a) at 292 nm to identify the peaks due to impurities A and B, the response at 292 nm being much higher than at 260 nm; use the chromatogram supplied with *fludarabine for peak identification CRS* and the chromatogram obtained with reference solution (d) at 260 nm to identify impurity C.

Relative retention With reference to fludarabine phosphate (retention time = about 9 min): impurity A = about 0.26; impurity B = about 0.34; impurity C = about 0.42.

System suitability Reference solution (a) at 292 nm:

— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Limits At 260 nm:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 4.0; impurity B = 2.5; impurity C = 1.9;

— *impurity A*: maximum 0.8 per cent;

— *impurity C*: maximum 0.4 per cent;

— *impurity B*: maximum 0.2 per cent;

— *unspecified impurities eluting before fludarabine phosphate*: for each impurity, maximum 0.10 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak eluting after fludarabine phosphate.

B. Late eluting impurities.

Conditions as described under Test A with the following modifications.

Mobile phase Mix 200 volumes of *methanol R* and 800 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R*.

Detection Spectrophotometer at 260 nm.

Injection 10 µL of test solution (a) and reference solutions (b) and (c).

Run time 8 times the retention time of the principal peak in the chromatogram obtained with test solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *fludarabine for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D, E and F.

Relative retention With reference to fludarabine phosphate (retention time = about 2.5 min): impurity D = about 1.5; impurity E = about 1.9; impurity F = about 2.5.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to fludarabine phosphate and impurity D.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.5; impurity E = 0.6; impurity F = 1.8;

— *impurity E*: maximum 0.2 per cent;

— *impurity F*: maximum 0.2 per cent;

— *impurity D*: maximum 0.15 per cent;

— *unspecified impurities eluting after fludarabine phosphate*: for each impurity, maximum 0.10 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak eluting before fludarabine phosphate.

Total of impurities eluting before fludarabine phosphate in test A, apart from impurities A, B and C, and after fludarabine phosphate in test B, apart from impurities D, E and F Maximum 0.5 per cent.

Total of all impurities eluting before fludarabine phosphate in test A and after fludarabine phosphate in test B Maximum 2.0 per cent.

Ethanol (*2.4.24, System A*)

Maximum 1.0 per cent.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.200 g (ground to a very fine powder). Stir the substance in 15 mL of *anhydrous methanol R* for about 15 s before titrating.

ASSAY

Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modifications.

Detection Spectrophotometer at 260 nm.

Injection 10 µL of test solution (b) and reference solution (e).

Calculate the percentage content of $C_{10}H_{13}FN_5O_7P$ taking into account the assigned content of *fludarabine phosphate CRS*.

www.webofpharma.com

https://thuocngocanh.com/

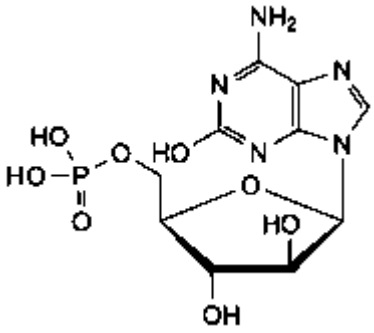
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

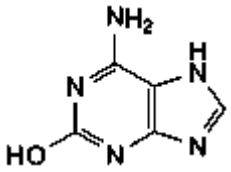
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

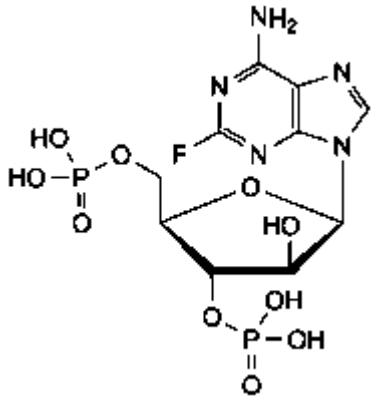
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *G, H, I, J.*



A. 6-amino-9-(5-*O*-phosphono-β-D-arabinofuranosyl)-9*H*-purin-2-ol,



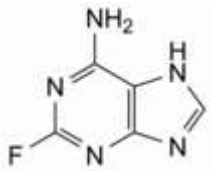
B. 6-amino-7*H*-purin-2-ol,



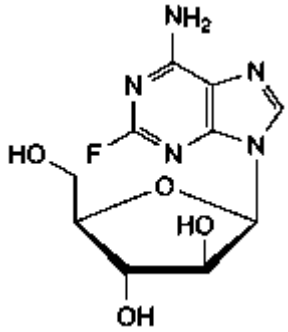
C. 9-(3,5-di-*O*-phosphono-β-D-arabinofuranosyl)-2-fluoro-9*H*-purin-6-amine,

www.webofpharma.com

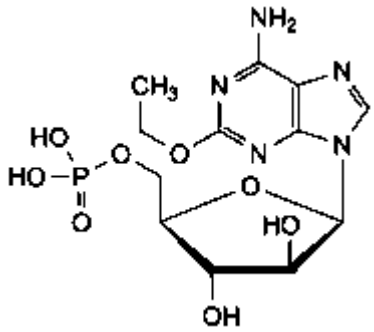
https://thuocngocanh.com/



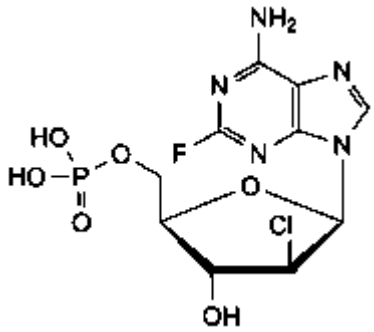
D. 2-fluoro-7*H*-purin-6-amine,



E. 9-β-D-arabinofuranosyl-2-fluoro-9*H*-purin-6-amine,



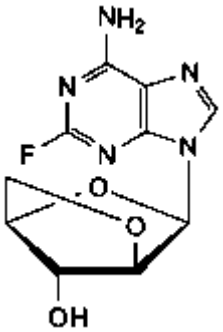
F. 2-ethoxy-9-(5-*O*-phosphono-β-D-arabinofuranosyl)-9*H*-purin-6-amine,



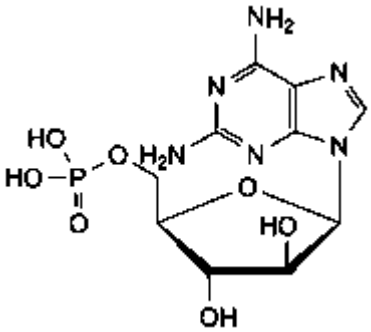
G. 9-(2-chloro-2-deoxy-5-*O*-phosphono-β-D-arabinofuranosyl)-2-fluoro-9*H*-purin-6-amine,

www.webofpharma.com

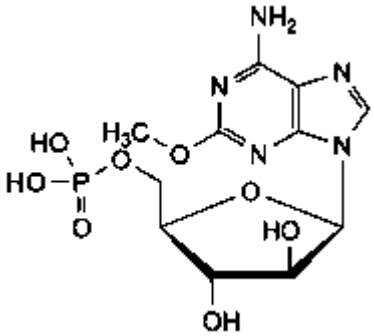
https://thuocngocanh.com/



H. 9-(2,5-anhydro-β-D-arabinofuranosyl)-2-fluoro-9*H*-purin-6-amine,



I. 9-(5-*O*-phosphono-β-D-arabinofuranosyl)-9*H*-purine-2,6-diamine,



J. 2-methoxy-9-(5-*O*-phosphono-β-D-arabinofuranosyl)-9*H*-purin-6-amine.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

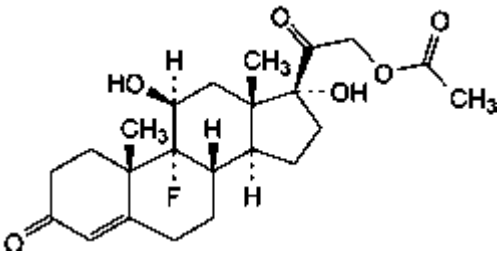
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fludrocortisone Acetate

General Notices

(Ph. Eur. monograph 0767)



$C_{23}H_{31}FO_6$ 422.5 *514-36-3*

Action and use

Mineralocorticoid.

Preparation

Fludrocortisone Tablets

Ph Eur

DEFINITION

9-Fluoro-11β,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

www.webofpharma.com

https://thietbiuocngocanh.com/

First identification: A, B.

Second identification: C, D, E.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *fludrocortisone acetate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *acetone R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Solvent mixture *methanol R*, *methylene chloride R* (1:9 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve 10 mg of *fludrocortisone acetate CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *cortisone acetate CRS* in 5 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *alcoholic solution of sulfuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

C. Thin-layer chromatography (2.2.27).

www.webofpharma.com

https://thuocngocanh.com/

Test solution (a) Dissolve 25 mg of the substance to be examined in *methanol R* and dilute to 5 mL with the same solvent (solution A). Dilute 2 mL of the solution to 10 mL with *methylene chloride R*.

Test solution (b) Transfer 2 mL of solution A to a 15 mL glass tube with a ground-glass stopper or a polytetrafluoroethylene cap. Add 10 mL of *saturated methanolic potassium hydrogen carbonate solution R* and immediately pass a stream of *nitrogen R* through the solution for 5 min. Stopper the tube. Heat on a water-bath at 45 °C protected from light for 2.5 h. Allow to cool.

Reference solution (a) Dissolve 25 mg of *fludrocortisone acetate CRS* in *methanol R* and dilute to 5 mL with the same solvent (solution B). Dilute 2 mL of the solution to 10 mL with *methylene chloride R*.

Reference solution (b) Transfer 2 mL of solution B to a 15 mL glass tube with a ground-glass stopper or a polytetrafluoroethylene cap. Add 10 mL of *saturated methanolic potassium hydrogen carbonate solution R* and immediately pass a stream of *nitrogen R* through the solution for 5 min. Stopper the tube. Heat on a water bath at 45 °C protected from light for 2.5 h. Allow to cool.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in each of the chromatograms obtained with the test solutions is similar in position and size to the principal spot in the chromatogram obtained with the corresponding reference solution.

Detection B Spray with *alcoholic solution of sulfuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in each of the chromatograms obtained with the test solutions is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with the corresponding reference solution. The principal spots in the chromatograms obtained with test solution (b) and reference solution (b) have R_F values distinctly lower than those of the principal spots in the chromatograms obtained with test solution (a) and reference solution (a).

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter and add to the filtrate a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The colour of the solution to be examined changes from red to yellow.

E. About 10 mg gives the reaction of acetyl (*2.3.1*).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Specific optical rotation (2.2.7)

+ 148 to + 156 (dried substance).

Dissolve 0.250 g in *dioxan R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of *fludrocortisone acetate CRS* and 2.0 mg of *hydrocortisone acetate CRS* in the mobile phase, then dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.2 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *tetrahydrofuran R*, *water R* (35:65 *V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Equilibration With the mobile phase for about 30 min.

Injection 20 µL.

Run time Twice the retention time of fludrocortisone acetate.

Retention time Hydrocortisone acetate = about 8.5 min; fludrocortisone acetate = about 10 min.

System suitability Reference solution (a):

— *resolution*: minimum 1.0 between the peaks due to hydrocortisone acetate and fludrocortisone acetate; if necessary, adjust slightly the concentration of tetrahydrofuran in the mobile phase (an increase in the concentration of tetrahydrofuran reduces the retention times).

Limits:

— *any impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

ASSAY

Dissolve 10.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (2.2.25) at the absorption maximum at 238 nm.

Calculate the content of $C_{23}H_{31}FO_6$ taking the specific absorbance to be 405.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fludrocortisone Tablets

General Notices

Action and use

Mineralocorticoid.

DEFINITION

Fludrocortisone Tablets contain Fludrocortisone Acetate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of fludrocortisone acetate, $C_{23}H_{31}FO_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent I* and *mobile phase B*. Apply separately to the plate 20 µL of each of the following solutions. For solution (1) shake a quantity of the powdered tablets containing 1 mg of fludrocortisone acetate with 20 mL of *chloroform* for 5 minutes, filter, evaporate the filtrate to dryness and dissolve the residue in 4 mL of a mixture of 9 volumes of *chloroform* and 1 volume of *methanol*. Solution (2) contains 0.025% w/v of *fludrocortisone acetate BPCRS* in a mixture of 9 volumes of *chloroform* and 1 volume of *methanol*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to fludrocortisone acetate in the chromatogram obtained with solution (2).

TESTS

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Fludrocortisone Acetate comply with the requirement stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light. Solution A contains 0.002% w/v of *norethisterone BPCRS* in *acetonitrile*.

(1) Place a single tablet in a centrifuge tube, add 1 mL of *water*, shake on a vortex-type mixer for 1 minute, add 4.0 mL of solution A and shake again for 1 minute. Shake for a further 40 minutes on a mechanical shaker, centrifuge and use the clear supernatant solution.

(2) 4 volumes of a 0.0025% w/v solution of *fludrocortisone acetate BPCRS* in solution A and 1 volume of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of *acetonitrile* and 60 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{31}FO_6$ in each tablet using the declared content of $C_{23}H_{31}FO_6$ in *fludrocortisone acetate BPCRS*.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution A contains 0.01% w/v of *norethisterone BPCRS* (internal standard) in *acetonitrile*.

(1) Shake a quantity of the powdered tablets containing 0.5 mg of fludrocortisone acetate with 2 mL of *water* for 1 minute, add 4 mL of solution A and 4 mL of *acetonitrile* and shake on a mechanical shaker for 40 minutes. Dilute the mixture to 20 mL with *acetonitrile*, centrifuge and use the supernatant liquid.

(2) 20 mL of solution A, 25 mL of a 0.01% w/v solution of *fludrocortisone acetate BPCRS* in *acetonitrile* and 10 mL of *water* diluted to 100 mL with *acetonitrile*.

(3) Prepare in the same manner as solution (1) but using 8 mL of *acetonitrile* in place of 4 mL of solution A and 4 mL of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{31}FO_6$ in the tablets using the declared content of $C_{23}H_{31}FO_6$ in *fludrocortisone acetate BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

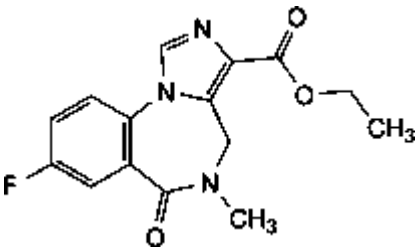
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flumazenil

General Notices

(Ph. Eur. monograph 1326)



$C_{15}H_{14}FN_3O_3$ 303.3 *78755-81-4*

Action and use

Benzodiazepine receptor antagonist.

Ph Eur

DEFINITION

Ethyl 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in methanol.

mp

198 °C to 202 °C.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of flumazenil*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and is not more intensely coloured than reference solution BY_7 (2.2.2, *Method II*).

Dissolve 0.10 g in *methanol R* and dilute to 10 mL with the same solvent.

Impurity C

Maximum 1 per cent.

Dissolve 0.10 g in 0.5 mL of *methylene chloride R* and dilute to 10 mL with *butanol R*. To 5.0 mL of this solution add 2.0 mL of *ninhydrin solution R* and heat in a water-bath at 95 °C for 15 min. Any blue-purple colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 5.0 mL of a 0.1 g/L solution of *dimethylformamide diethylacetal R* in *butanol R*.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in 5 mL of *methanol R* and dilute to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 2.0 mg of *flumazenil impurity B CRS* and 2.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 25.0 mL with the mobile phase.

Reference solution (b) Dilute 10.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase To 800 mL of *water R* adjusted to pH 2.0 with *phosphoric acid R*, add 130 mL of *methanol R* and 70 mL of *tetrahydrofuran R* and mix.

Flow rate 1 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Run time 3 times the retention time of flumazenil.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to flumazenil (retention time = about 14 min): impurity A = about 0.4; impurity D = about 0.5; impurity E = about 0.6; impurity B = about 0.7; impurity F = about 2.4.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity B and flumazenil.

Limits:

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.250 g in 50 mL of a mixture of 2 volumes of *acetic anhydride R* and 3 volumes of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 30.33 mg of $C_{15}H_{14}FN_3O_3$.

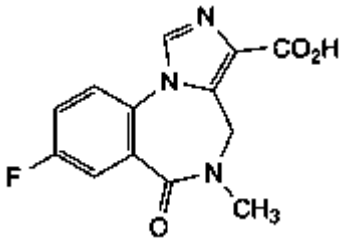
IMPURITIES

Specified impurities *B, C.*

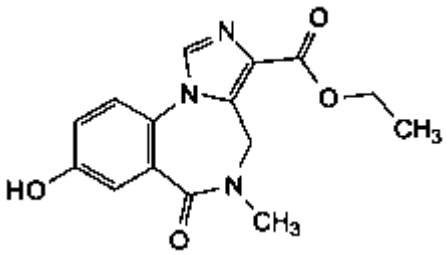
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, D, E, F.*

www.webofpharma.com

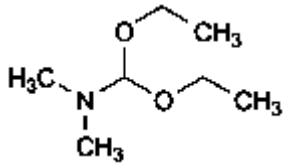
https://thuocngocanh.com/



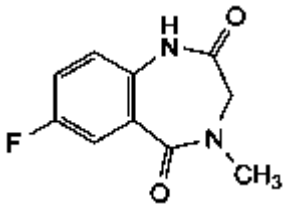
A. 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid,



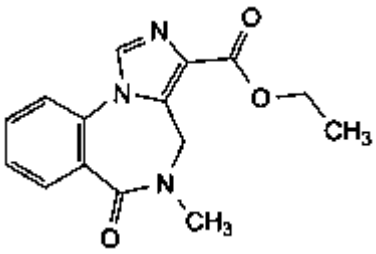
B. ethyl 8-hydroxy-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate,



C. diethoxy-*N*,*N*-dimethylmethanamine,



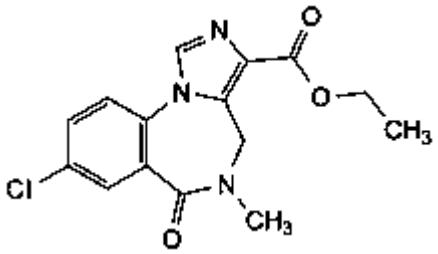
D. 7-fluoro-4-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione,



E. ethyl 5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate,

www.webofpharma.com

https://thuocngocanh.com/



F. ethyl 8-chloro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

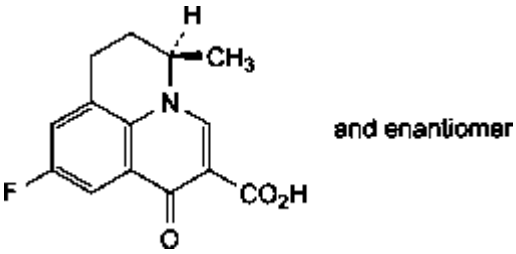
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flumequine

General Notices

(Ph. Eur. monograph 1517)



$C_{14}H_{12}FNO_3$ 261.3 *42835-25-6*

Action and use

Antibacterial.

Ph Eur

DEFINITION

(*RS*)-9-Fluoro-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, microcrystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble in methanol. It is freely soluble in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flumequine CRS*.

B. Optical rotation (see Tests).

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in 10 mL of *methylene chloride R*.

Reference solution Dissolve 5 mg of *flumequine CRS* in 10 mL of *methylene chloride R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *ammonia R*, *water R*, *ethanol (96 per cent) R* (10:10:90 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 2 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter and add to the filtrate a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution changes from red to yellow and the blank remains red.

TESTS

Solution S

Dissolve 5.00 g in *0.5 M sodium hydroxide* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

Optical rotation (2.2.7)

-0.10° to + 0.10°, determined on solution S.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 35.0 mg of the substance to be examined in *dimethylformamide R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve the contents of a vial of *flumequine impurity B CRS* in 2.0 mL of a 50 µg/mL solution of *flumequine CRS* in *dimethylformamide R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 200.0 mL with *dimethylformamide R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, 1.36 g/L solution of *potassium dihydrogen phosphate R* (49:51 *V/V*).

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 313 nm.

Injection 10 µL; inject *dimethylformamide R* as a blank.

Run time 3 times the retention time of flumequine.

Relative retention With reference to flumequine (retention time = about 13 min): impurity A = about 0.67; impurity B = about 0.85.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity B and flumequine.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (2.4.14)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

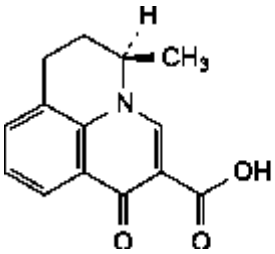
ASSAY

Dissolve 0.500 g in 50 mL of *dimethylformamide R*. Titrate with 0.1 M tetrabutylammonium hydroxide, determining the end-point potentiometrically (*2.2.20*).

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 26.13 mg of $C_{14}H_{12}FNO_3$.

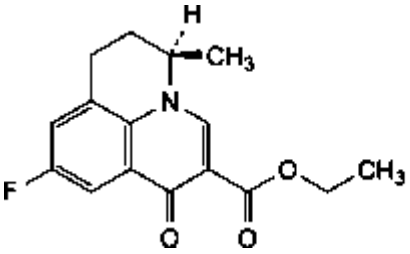
IMPURITIES

Specified impurities *A, B.*



and enantiomer

A. (*RS*)-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid (defluoroflumequine),



and enantiomer

B. ethyl (*RS*)-9-fluoro-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylate (flumequine ethyl ester).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flumetasone and Clioquinol Ear Drops

General Notices

Action and use

Glucocorticoid and antibacterial.

DEFINITION

Flumetasone and Clioquinol Ear Drops contain Flumetasone Pivalate and Clioquinol.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of flumetasone pivalate, $C_{27}H_{36}F_2O_6$

95.0 to 105.0% w/v of the stated amount.

Content of clioquinol, C_9H_5ClINO

95.0 to 105.0% w/v of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the ear drops containing 1 mg of Flumetasone Pivalate in *acetone*, add sufficient *acetone* to produce 10 mL and filter.

(2) 0.01% w/v of *flumetasone pivalate BPCRS* in *acetone*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 50 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, heat at 105° for 5 minutes and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1.2 volumes of *water*, 8 volumes of *methanol*, 15 volumes of *ether* and 77 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay for flumetasone pivalate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to flumetasone pivalate in the chromatogram obtained with solution (2).

C. In the Assay for clioquinol, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to clioquinol in the chromatogram obtained with solution (2).

TESTS

Related substances

For flumetasone pivalate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *methanol (80%)*.

(1) Shake a volume of the ear drops containing 1.2 mg of Flumetasone Pivalate with 50 mL of *methanol (80%)*, add 40 mg of *copper(II) acetate* and dilute to 100 mL. Place the solution in an ice bath for 1 hour, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.001% w/v of *flumetasone pivalate BPCRS* and 0.00001% w/v of *flumetasone acetate*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 235 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of flumetasone pivalate.

MOBILE PHASE

0.2 volumes of *glacial acetic acid*, 20 volumes of *acetonitrile*, 40 volumes of *methanol* and 40 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to flumetasone acetate and flumetasone pivalate is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

www.webofpharma.com

https://thuocngocanh.com/

Disregard any peak:

that elutes before 1.5 minutes;

with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

For clioquinol

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.1 volume of *orthophosphoric acid*, 10 volumes of *water*, 30 volumes of *acetonitrile* and 60 volumes of *methanol*.

(1) Dilute a volume of the ear drops containing 18 mg of Clioquinol with 1 mL of *tetrahydrofuran*, add sufficient solution A to produce 100 mL, centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) Dilute 1 volumes of solution (2) to 5 volumes with solution A.
(4) 0.018% w/v of *clioquinol BPCRS* and 0.00018% w/v each of *5-chloroquinolin-8-ol, 5,7-dichloroquinolin-8-ol* and *5,7-diiodoquinolin-8-ol* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 260 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of the peak due to clioquinol.

MOBILE PHASE

20 volumes of *water* and 80 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to clioquinol (retention time about 5 min) are: 5-chloroquinolin-8-ol, about 0.6; 5,7-diiodoquinolin-8-ol, about 0.8 and 5,7-dichloroquinolin-8-ol, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to clioquinol and 5,7-dichloroquinolin-8-ol is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 5-chloroquinolin-8-ol is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to 5,7-diiodoquinolin-8-ol or 5,7-dichloroquinolin-8-ol is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than half that of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

For flumetasone pivalate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a weighed quantity of the ear drops containing 1.2 mg of Flumetasone Pivalate with 25 mL of the mobile phase, add 30 mg of *copper(II) acetate* and dilute to 50 mL with the mobile phase. Place the solution in an ice bath for 1 hour, centrifuge and use the supernatant liquid.

(2) 0.0024% w/v of *flumetasone pivalate BPCRS* in the mobile phase.

(3) 0.001% w/v of *flumetasone pivalate BPCRS* and 0.00001% w/v of *flumetasone acetate* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of *water* and 80 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to flumetasone acetate and flumetasone pivalate is at least 1.5. If necessary adjust the concentration of *methanol* in the mobile phase.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the ear drops, Appendix V G, and calculate the content of $C_{27}H_{36}F_2O_6$, weight in volume, using the declared content of $C_{27}H_{36}F_2O_6$ in *flumetasone pivalate BPCRS*.

For clioquinol

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a weighed quantity of the ear drops containing 18 mg of Clioquinol add 5 mL of a solution containing 1 volume of *triethylamine* and 1 volume of *tetrahydrofuran*, add sufficient of the mobile phase to produce 50 mL and centrifuge. Dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.

(2) 0.0036% w/v of *clioquinol BPCRS* in the mobile phase.

(3) 0.0002% w/v of *clioquinol BPCRS* and 0.0004% w/v of *5,7-dichloroquinolin-8-ol* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 256 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

0.1 volume of *orthophosphoric acid*, 10 volumes of *water*, 30 volumes of *acetonitrile* and 60 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between clioquinol and 5,7-dichloroquinolin-8-ol is at least 1.5. If necessary adjust the concentration of *methanol* in the mobile phase.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the ear drops, Appendix V G, and calculate the content of C_9H_5ClINO, weight in volume, using the declared content of C_9H_5ClINO in *clioquinol BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

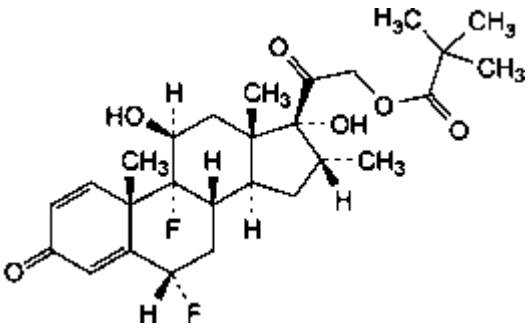
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flumetasone Pivalate

General Notices

(Ph. Eur. monograph 1327)



$C_{27}H_{36}F_2O_6$ 494.6 *2002-29-1*

Action and use

Glucocorticoid.

Preparation

Flumetasone and Clioquinol Ear Drops

Ph Eur

DEFINITION

6α,9-Difluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate.

Content

97.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent) and in methylene chloride.

www.webofpharma.com

https://thuvienthuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flumetasone pivalate CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *flumetasone pivalate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *desoxycortone acetate CRS* in *acetone R* and dilute to 10 mL with the same solvent. Dilute 5 mL of this solution to 10 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *alcoholic solution of sulfuric acid R*. Heat at 120 °C for 10 min or until the spots appear. Allow to cool. Examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

www.webofpharma.com

https://thuocngocanh.com/

C. Add about 2 mg to 2 mL of a mixture of 0.5 mL of *water R* and 1.5 mL of *sulfuric acid R* and shake to dissolve. Within 5 min, a pink colour develops. Add this solution to 10 mL of *water R* and mix. The colour fades and a clear solution remains.

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter. To a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R* add 1.0 mL of the filtrate. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Solution S

Dissolve 0.50 g in *acetone R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

+ 69 to + 77 (dried substance), determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 10 mg of *dexamethasone pivalate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. To 5.0 mL of this solution, add 5.0 mL of the test solution, mix and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *tetrahydrofuran R*, *acetonitrile R*, *water R*, *methanol R* (5:30:30:35 *V/V/V/V*).

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

www.webofpharma.com

https://thietbiuocngocanh.com/

Run time 1.5 times the retention time of flumetasone pivalate.

Relative retention With reference to flumetasone pivalate: impurity C = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 2.8 between the peaks due to flumetasone pivalate and impurity C; if necessary, adjust the concentration of tetrahydrofuran in the mobile phase.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent);

— *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 4 h.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (2.2.25) at the absorption maximum at 239 nm.

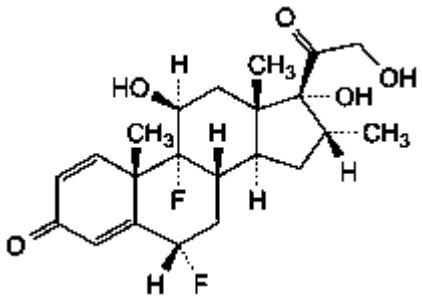
Calculate the content of $C_{27}H_{36}F_2O_6$ taking the specific absorbance to be 336.

STORAGE

Protected from light.

IMPURITIES

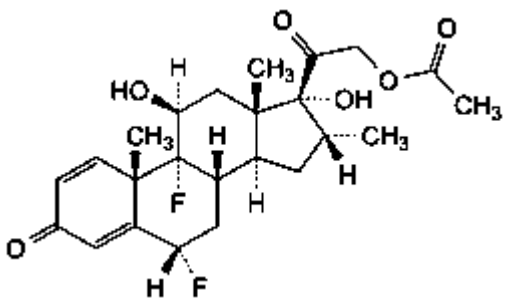
Specified impurities *A, B, C, D*.



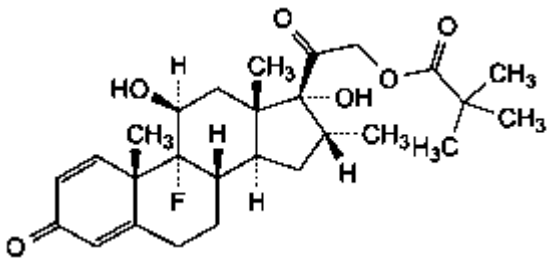
A. 6α,9-difluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (flumetasone),

www.webofpharma.com

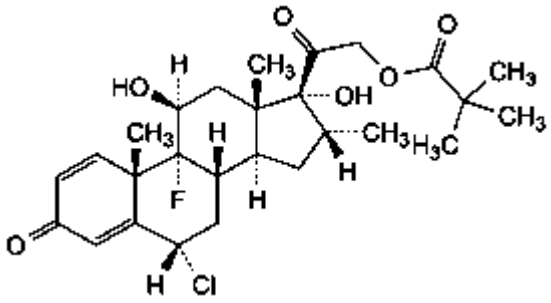
https://thuocngocanh.com/



B. 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (flumetasone acetate),



C. 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate (dexamethasone pivalate),



D. 6α-chloro-9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate (chlordexamethasone pivalate).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

https://thuocngocanh.com/

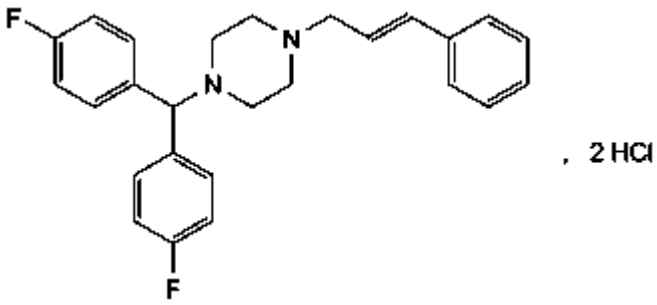
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.2 (effective 01/07/2023)

Flunarizine Dihydrochloride

General Notices

(Ph. Eur. monograph 1722)



$C_{26}H_{28}Cl_2F_2N_2$ 477.4 *30484-77-6*

Action and use

Calcium channel blocker.

Ph Eur

DEFINITION

1-[Bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazine dihydrochloride.

Content

99.0 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flunarizine dihydrochloride CRS*.

B. Dissolve 25 mg in 2 mL of *methanol R* and add 0.5 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *flunarizine for system suitability CRS* (containing impurities B and C) in *methanol R* and dilute to 1 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: solution containing 23.8 g/L of *tetrabutylammonium hydrogen sulfate R* and 7 g/L of *ammonium acetate R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	80 → 40	20 → 60
12 - 15	40	60

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *flunarizine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities B and C.

Relative retention With reference to flunarizine (retention time = about 8 min): impurity B = about 0.93; impurity C = about 0.96.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to flunarizine.

Calculation of percentage contents:

— for each impurity, use the concentration of flunarizine dihydrochloride in reference solution (b).

Limits:

— *impurity B*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.200 g in 70 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added at the second point of inflexion. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 23.87 mg of $C_{26}H_{28}Cl_2F_2N_2$.

STORAGE

In an airtight container, protected from light.

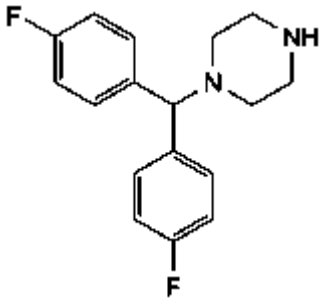
IMPURITIES

Specified impurities *B*.

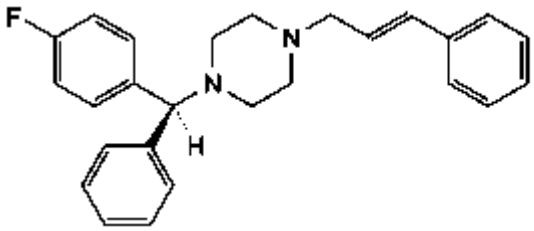
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D*.

www.webofpharma.com

https://thuocngocanh.com/

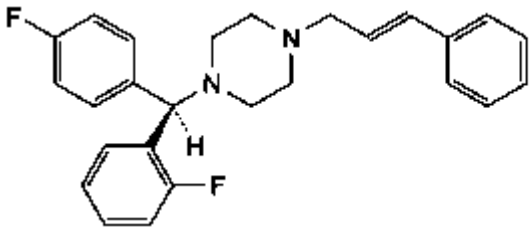


A. 1-[bis(4-fluorophenyl)methyl]piperazine,



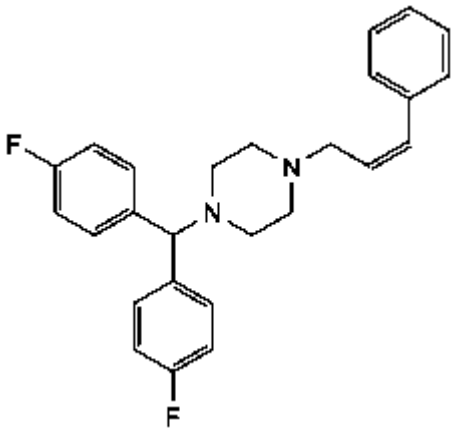
and enantiomer

B. 1-[(*RS*)-(4-fluorophenyl)phenylmethyl]-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazine,



and enantiomer

C. 1-[(*RS*)-(2-fluorophenyl)(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazine,



D. 1-[bis(4-fluorophenyl)methyl]-4-[(2*Z*)-3-phenylprop-2-en-1-yl]piperazine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

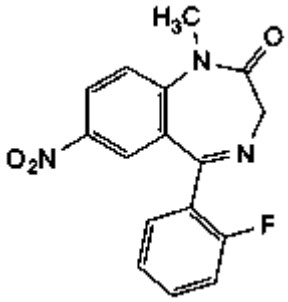
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Flunitrazepam

General Notices

(Ph. Eur. monograph 0717)



$C_{16}H_{12}FN_3O_3$ 313.3 *1622-62-4*

Action and use

Benzodiazepine.

Ph Eur

DEFINITION

5-(2-Fluorophenyl)-1-methyl-7-nitro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of flunitrazepam*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 100.0 mg of the substance to be examined in 10 mL of *acetonitrile R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 4 mg of the substance to be examined and 4 mg of *nitrazepam R* in 5 mL of *acetonitrile R* and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R*, *acetonitrile R*, *water R* (50:305:645 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 6 times the retention time of flunitrazepam.

Relative retention With reference to flunitrazepam (retention time = about 11 min): impurity A = about 0.2; impurity B = about 0.6; impurity C = about 2.3; impurity D = about 4.0.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to nitrazepam and flunitrazepam.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2.44,

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

www.webofpharma.com

https://thuocngocanh.com/

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

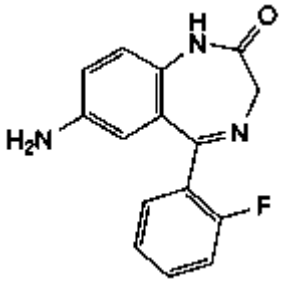
Dissolve 0.250 g in 20 mL of *anhydrous acetic acid R* and add 50 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 31.33 mg of $C_{16}H_{12}FN_3O_3$.

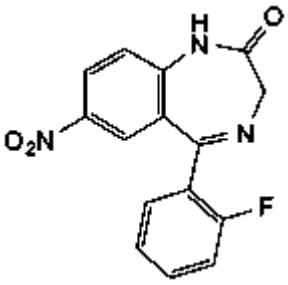
STORAGE

Protected from light.

IMPURITIES



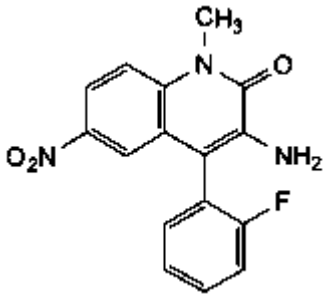
A. 7-amino-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (7-aminodemethylflunitrazepam),



B. 5-(2-fluorophenyl)-7-nitro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (demethylflunitrazepam),

www.webofpharma.com

https://thuocngocanh.com/



C. 3-amino-4-(2-fluorophenyl)-1-methyl-6-nitroquinolin-2(1*H*)-one,

D. (2-fluorophenyl)[2-(methylamino)-5-nitrophenyl]methanone.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

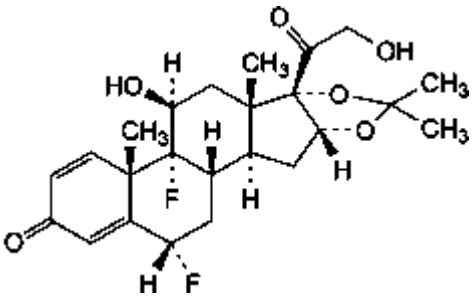
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluocinolone Acetonide

General Notices

(Ph. Eur. monograph 0494)



$C_{24}H_{30}F_2O_6$ 452.5 *67-73-2*

Action and use

Glucocorticoid.

Preparations

Fluocinolone Cream

Fluocinolone Ointment

Ph Eur

DEFINITION

6α,9-Difluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone and in anhydrous ethanol, practically insoluble in heptane.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *fluocinolone acetonide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (d).

TESTS

Specific optical rotation (2.2.7)

+ 100 to + 104 (dried substance).

Dissolve 0.100 g in *anhydrous ethanol R* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from lightand prepare the solutions immediately before use.*

Solvent mixture *acetonitrile R*, *water R* (20:80 *V/V*).

Buffer solution Dissolve 5.68 g of *anhydrous disodium hydrogen phosphate R* and 3.63 g of *potassium dihydrogen phosphate R* in *water R* and dilute to 1000.0 mL with the same solvent.

Test solution (a) Dissolve 20.0 mg of the substance to be examined in 20 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *fluocinolone acetonide for system suitability CRS* (containing impurities H, J and K) in 2 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*.

Reference solution (b) Dissolve 2 mg of *fluocinolone acetonide for peak identification CRS* (containing impurities D and I) in 2 mL of *acetonitrile R* and dilute to 10.0 mL with *water R*.

Reference solution (c) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of *fluocinolone acetonide CRS* in 20 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, buffer solution (28:72 *V/V*);

— *mobile phase B*: *water R*, *acetonitrile R* (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 42	100 → 0	0 → 100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 238 nm.

Injection 40 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *fluocinolone acetonide for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities H, J and K; use the chromatogram supplied with *fluocinolone acetonide for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities D and I.

Relative retention With reference to fluocinolone acetonide (retention time = about 18 min): impurity D = about 0.8; impurity H = about 0.90; impurity I = about 0.94; impurity J = about 1.05; impurity K = about 1.2.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity J and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to fluocinolone acetonide.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity K by 1.3;

— for each impurity, use the concentration of fluocinolone acetonide in reference solution (c).

Limits:

— *impurity K*: maximum 0.3 per cent;

— *impurities D, J*: for each impurity, maximum 0.2 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *impurities H, I*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.7 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 20 µL of test solution (b) and reference solution (d).

Calculate the percentage content of $C_{24}H_{30}F_2O_6$ taking into account the assigned content of *fluocinolone acetonide CRS*.

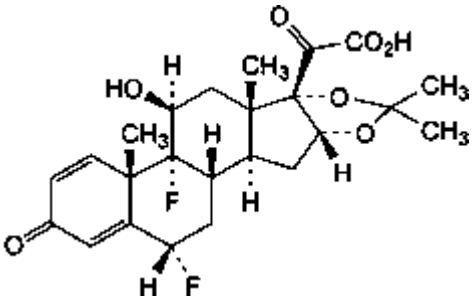
STORAGE

Protected from light.

IMPURITIES

Specified impurities *D, H, I, J, K.*

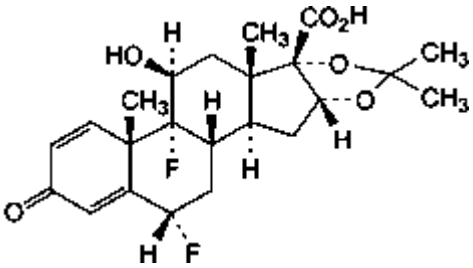
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E, F, G, L, M.*



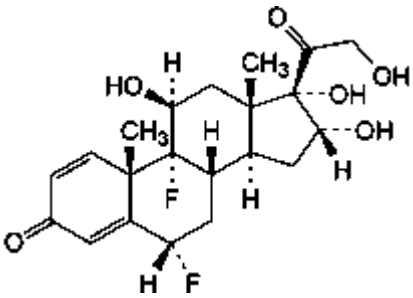
A. 6α,9-difluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3,20-dioxopregna-1,4-dien-21-oic acid,

www.webofpharma.com

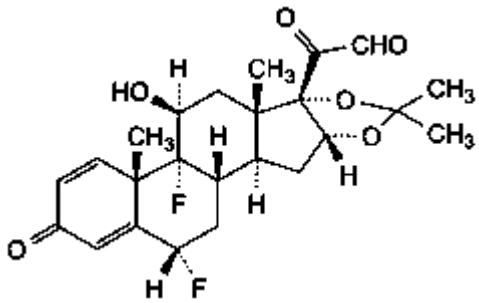
https://thuocngocanh.com/



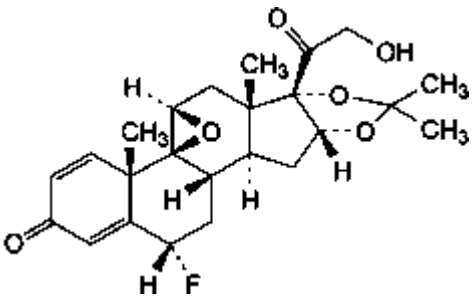
B. 6α,9-difluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3-oxoandrosta-1,4-diene-17β-carboxylic acid,



C. 6α,9-difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (fluocinolone),



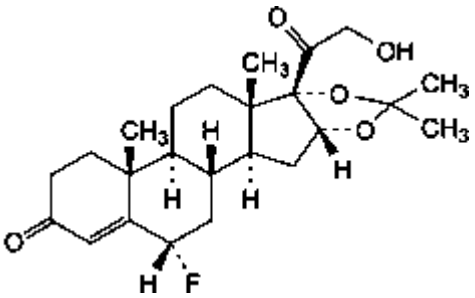
D. 6α,9-difluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3,20-dioxopregna-1,4-dien-21-al,



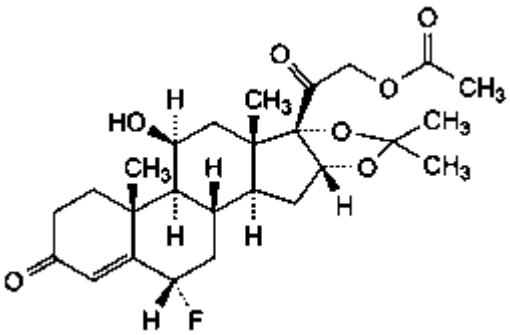
E. 9,11β-epoxy-6α-fluoro-21-hydroxy-16α,17-(1-methylethylidenedioxy)-9β-pregna-1,4-diene-3,20-dione,

www.webofpharma.com

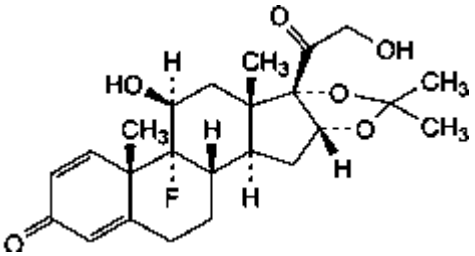
https://thuocngocanh.com/



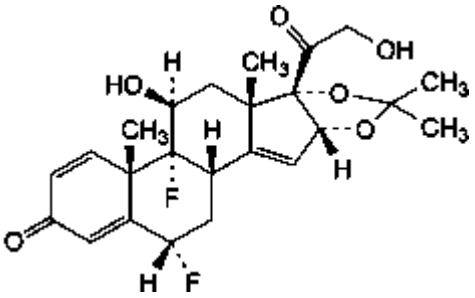
F. 6α-fluoro-21-hydroxy-16α,17-(1-methylethylidenedioxy)pregn-4-ene-3,20-dione,



G. 6α-fluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3,20-dioxopregn-4-en-21-yl acetate,



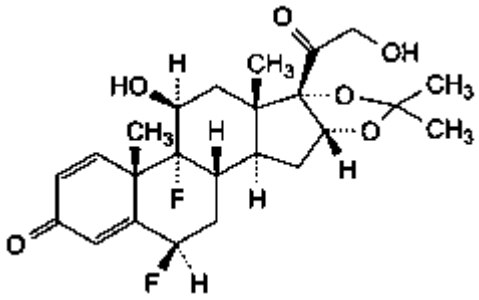
H. 9-fluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione,



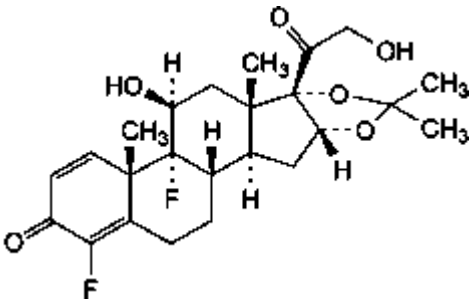
I. 6α,9-difluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4,14-triene-3,20-dione,

www.webofpharma.com

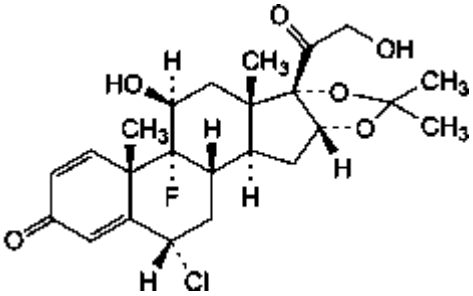
https://thuocngocanh.com/



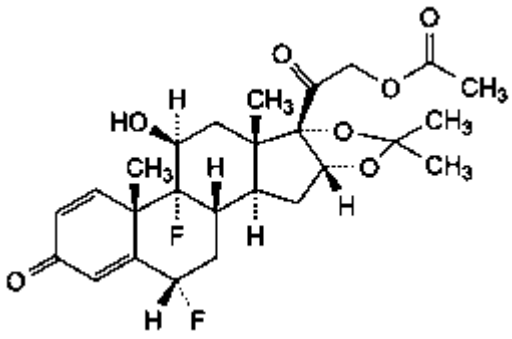
J. 6β,9-difluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione,



K. 4,9-difluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione,



L. 6α-chloro-9-fluoro-11β,21-dihydroxy-16α,17-(1-methylethylidenedioxy)pregna-1,4-diene-3,20-dione,



M. 6α,9-difluoro-11β-hydroxy-16α,17-(1-methylethylidenedioxy)-3,20-dioxopregna-1,4-dien-21-yl acetate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

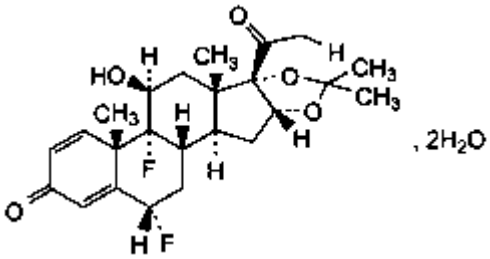
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluocinolone Acetonide Dihydrate

General Notices



$C_{24}H_{30}F_2O_6,2H_2O$ 488.5 (anhydrous) *67-73-2*

Action and use

Glucocorticoid.

Preparations

Fluocinolone Cream

Fluocinolone Ointment

DEFINITION

Fluocinolone Acetonide Dihydrate is 6α,9α-difluoro-11β,21-dihydroxy-16α-,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione dihydrate. It contains not less than 96.0% and not more than 104.0% of $C_{24}H_{30}F_2O_6$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

A white or almost white, crystalline powder.

Practically insoluble in *water*; freely soluble in *acetone*; soluble in *absolute ethanol*; sparingly soluble in *dichloromethane* and in *methanol*; practically insoluble in *hexane*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of fluocinolone acetonide dihydrate *(RS 147)*.

B. Complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent I* and *mobile phase H*. Apply 5 µL of each of the three solutions.

www.webofpharma.com

https://thuocngocanh.com/

C. Complies with the test for *identification of steroids*, Appendix III A, using the conditions specified in test B but using solutions prepared in the following manner. For solution (1) dissolve 10 mg in 1.5 mL of *glacial acetic acid* in a separating funnel, add 0.5 mL of a 2% w/v solution of *chromium(VI) oxide* and allow to stand for 30 minutes. Add 5 mL of *water* and 2 mL of *dichloromethane* and shake vigorously for 2 minutes. Allow to separate and use the lower layer. Prepare solution (2) in the same manner but using 10 mg of *fluocinolone acetonide BPCRS*.

TESTS

Light absorption

Dissolve 15 mg in sufficient *absolute ethanol* to produce 100 mL. Dilute 10 mL of the solution to 100 mL with *absolute ethanol*. The A(1%, 1 cm) of the resulting solution at the maximum at 239 nm is 345 to 375, calculated with reference to the anhydrous substance, Appendix II B.

Specific optical rotation

In a 1% w/v solution in *1,4-dioxan*, +92 to +96, calculated with reference to the anhydrous substance, Appendix V F.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) 0.25% w/v of the substance being examined in *acetonitrile*.
(2) 0.025% w/v each of *fluocinolone acetonide BPCRS* and *triamcinolone acetonide BPCRS* in 45% w/v of *acetonitrile*.
(3) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.
(4) Dilute 1 volume of solution (3) to 20 volumes with *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 238 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to triamcinolone acetonide and fluocinolone acetonide is at least 3.0;

www.webofpharma.com

https://thuocngocanh.com/

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* of the principal peak is at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the area of not more than one *secondary peak* is greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (3) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Water

7.0 to 8.5% w/w, Appendix IX C. Use 0.5 g.

ASSAY

Carry out the *tetrazolium assay of steroids*, Appendix VIII J, and calculate the content of $C_{24}H_{30}F_2O_6$ from the *absorbance* obtained by repeating the operation using *fluocinolone acetonide BPCRS* in place of the substance being examined.

STORAGE

Fluocinolone Acetonide Dihydrate should be protected from light.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluocinolone Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluocinolone Cream contains Fluocinolone Acetonide or Fluocinolone Acetonide Dihydrate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of fluocinolone acetonide, $C_{24}H_{30}F_2O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse, by shaking, a quantity of the preparation being examined containing 0.25 mg of Fluocinolone Acetonide in 2 mL of *chloroform*, add 10 mL of *methanol*, shake vigorously, cool in ice for 15 minutes, centrifuge at 3000 revolutions per minute for 15 minutes, decant the clear, supernatant liquid, evaporate to dryness on a water bath in a current of nitrogen and dissolve the residue in 1 mL of *chloroform*.

(2) 0.025% w/v solution of *fluocinolone acetonide BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air until the solvent has evaporated, heat at 105° for 5 minutes and spray whilst hot with *alkaline tetrazolium blue solution*.

MOBILE PHASE

1 volume of *triethylamine*, 10 volumes of *methanol*, 40 volumes of *chloroform* and 60 volumes of n-*hexane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to fluocinolone acetonide in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

For creams containing 0.025% to 0.2% w/w of fluocinolone acetonide

(1) 0.025% w/v of *fluocinolone acetonide BPCRS* and 0.005% w/v of *phenacetin* (internal standard) in *chloroform*.

(2) To a quantity of the cream containing 2.5 mg of Fluocinolone Acetonide add 60 mL of a solution prepared by adding 80 mL of *methanol* to 20 mL of a 25% w/v solution of *lithium chloride* and disperse by shaking vigorously. Add 100 mL of *cyclohexane*, shake gently for 2 minutes and separate the lower, aqueous methanolic layer, taking care to exclude any solid matter that separates at the interface. Repeat the extraction using a further 25 mL of the lithium chloride solution. To the combined extracts add a solution of 11 g of *aluminium potassium sulfate* in 214 mL of *water* followed by 50 mL of *chloroform*, shake vigorously for about 3 minutes, allow the layers to separate and filter the chloroform extract through filter paper (Whatman No. 1 is suitable), previously moistened with *chloroform*, again excluding any solid matter at the interface. Repeat the extraction with 50- and 10-mL quantities of *chloroform*, filtering the extracts as before. Evaporate the combined extracts to dryness on a water bath in a current of nitrogen, dissolve the residue in 5 mL of *chloroform*, transfer to a 10-mL graduated flask with the aid of *chloroform* and add sufficient *chloroform* to produce 10 mL.

(3) Prepare in the same manner as solution (2) but add 1.0 mL of a 0.050% w/v solution of *phenacetin* to the *chloroform* solution before dilution to 10 mL.

For creams containing 0.01% w/w of fluocinolone acetonide

(1) 0.01% w/v of *fluocinolone acetonide BPCRS* and 0.002% w/v of *phenacetin* (internal standard) in *chloroform*.

(2) Prepare as described above but using a quantity of the cream containing 1 mg of Fluocinolone Acetonide.

(3) Prepare in the same manner as solution (2) but add 1 mL of a 0.02% w/v solution of *phenacetin* to the *chloroform* solution before diluting to 10 mL.

For creams containing 0.00625% w/w of fluocinolone acetonide

(1) 0.00625% w/v of *fluocinolone acetonide BPCRS* and 0.00125% w/v of *phenacetin* (internal standard) in *chloroform*.

(2) Prepare as described above but using a quantity of the cream containing 0.62 mg of Fluocinolone Acetonide.

(3) Prepare in the same manner as solution (2) but add 1 mL of a 0.0125% w/v solution of *phenacetin* to the *chloroform* solution before diluting to 10 mL.

For creams containing 0.0025% w/w of fluocinolone acetonide

(1) 0.0025% w/v of *fluocinolone acetonide BPCRS* and 0.0005% w/v of *phenacetin* (internal standard) in *chloroform*.

(2) Prepare as described above but using a quantity of the cream containing 0.25 mg of Fluocinolone Acetonide.

(3) Prepare in the same manner as solution (2) but add 1 mL of a 0.005% w/v solution of *phenacetin* to the *chloroform* solution before diluting to 10 mL.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (20 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 243 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

58 volumes of *hexane*, 40 volumes of *chloroform*, 2 volumes of *methanol* and 0.1 volume of *glacial acetic acid*.

SYSTEM SUITABILITY

The assay is not valid unless the *resolution factor* (R_s) between the peaks due to fluocinolone acetonide and phenacetin is more than 2, and the *capacity factors* (*k'*) of fluocinolone acetonide and phenacetin are about 3 and 2, respectively. If these conditions are not achieved, adjust the concentration of *methanol* in the mobile phase, increasing its concentration to reduce the value of *k'* and reducing its concentration to increase the value of *k'*. If the correct values cannot be obtained by this means, the column is faulty and must be repacked. If, when the correct *k'* values have been obtained, the value of R_s is less than 2, reduce the concentration of *chloroform* in the mobile phase by 5% to obtain an increased retention time for both fluocinolone acetonide and phenacetin and re-adjust the *k'* values to the specified values by increasing the concentration of *methanol*. Repeat the adjustment of chloroform and methanol concentrations until correct values for both R_s and *k'* have been obtained.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{30}F_2O_6$ in the cream using the declared content of $C_{24}H_{30}F_2O_6$ in *fluocinolone acetonide BPCRS*.

LABELLING

When the active ingredient is Fluocinolone Acetonide Dihydrate, the quantity is stated in terms of the equivalent amount of fluocinolone acetonide.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluocinolone Ointment

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluocinolone Ointment contains Fluocinolone Acetonide or Fluocinolone Acetonide Dihydrate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of fluocinolone acetonide, $C_{24}H_{30}F_2O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 60 volumes of n-*hexane*, 40 volumes of *chloroform*, 10 volumes of *methanol* and 1 volume of *triethylamine* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) disperse, by shaking, a quantity of the preparation being examined containing 0.25 mg of fluocinolone acetonide in 2 mL of *chloroform*, add 10 mL of *methanol*, shake vigorously, cool in ice for 15 minutes, centrifuge at 3000 revolutions per minute for 15 minutes, decant the clear, supernatant liquid, evaporate to dryness on a water bath in a current of nitrogen and dissolve the residue in 1 mL of *chloroform*. Solution (2) contains 0.025% w/v solution of *fluocinolone acetonide BPCRS* in *chloroform*. After removal of the plate, allow it to dry in air until the solvent has evaporated, heat at 105° for 5 minutes and spray whilst hot with *alkaline tetrazolium blue solution*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay the chromatogram obtained with solution (3) shows a peak with the same retention time as the peak due to fluocinolone acetonide in the chromatogram obtained with solution (1).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Solution (1) contains 0.0050% w/v of *fluocinolone acetonide BPCRS* and 0.40% v/v of *toluene* (internal standard) in *methanol (80%)*.

For ointments containing 0.01% w/w or less of fluocinolone acetonide prepare solution (2) in the following manner. To a quantity of the ointment containing 0.5 mg of fluocinolone acetonide add 50 mL of *2,2,4-trimethylpentane* and 8 mL of *methanol (80%)*, warm gently on a water bath until the preparation is dispersed and shake vigorously for 2 minutes. Separate the lower, aqueous methanolic layer and wash the upper layer with 1 mL of *methanol (80%)*, adding the washing to the previous extract. To the combined extracts add sufficient *methanol*

www.webofpharma.com

https://thuocngocanh.com/

(80%) to produce 10 mL. Prepare solution (3) in the same manner as solution (2) but adding 1 mL of a 4% v/v solution of the internal standard in *methanol* to the combined extracts before dilution to 10 mL.

For ointments containing 0.025% w/w of fluocinolone acetonide, prepare solution (2) in the following manner. To a quantity of the ointment containing 1.25 mg of fluocinolone acetonide add 50 mL of *2,2,4-trimethylpentane* and 20 mL of *methanol (80%)*, warm gently on a water bath until the preparation is dispersed and shake vigorously for 2 minutes. Separate the lower, aqueous methanolic layer and wash the upper layer with 2 mL of *methanol (80%)*, adding the washing to the previous extract. To the combined extracts add sufficient *methanol (80%)* to produce 25 mL. Prepare solution (3) in the same manner as solution (2) but adding 1 mL of a 10% v/v solution of the internal standard in *methanol* to the combined extracts before dilution to 25 mL.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable), (b) a mixture of 55 volumes of *water*, 45 volumes of *acetonitrile* and 0.1 volume of *glacial acetic acid* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 238 nm.

Calculate the content of $C_{24}H_{30}F_2O_6$ in the ointment using the declared content of $C_{24}H_{30}F_2O_6$ in *fluocinolone acetonide BPCRS*.

LABELLING

When the active ingredient is Fluocinolone Acetonide Dihydrate, the quantity is stated in terms of the equivalent amount of fluocinolone acetonide.

© Crown Copyright 2022

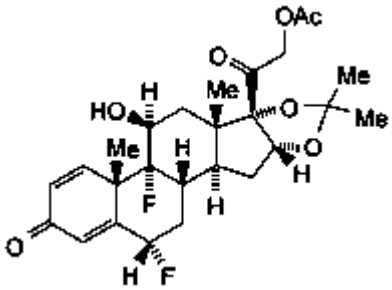
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluocinonide

General Notices



$C_{26}H_{32}F_2O_7$ 494.5 *356-12-7*

Action and use

Glucocorticoid.

Preparations

Fluocinonide Cream

Fluocinonide Ointment

DEFINITION

Fluocinonide is 6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-3,20-dioxopregna-1,4-dien-21-yl acetate. It contains not less than 97.0% and not more than 103.0% of $C_{26}H_{32}F_2O_7$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white, crystalline powder.

Practically insoluble in *water*; slightly soluble in *absolute ethanol*. It melts at about 220°, with decomposition.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of fluocinonide *(RS 148)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 12 volumes of *water*, 80 volumes of *methanol*, 150 volumes of *ether* and 770 volumes of *dichloromethane* as the mobile phase; mix the water and the methanol before adding to the remaining components of the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) dissolve 25 mg of the substance being examined in

www.webofpharma.com

https://thuocngocanh.com/

5 mL of *methanol* (solution A); dilute 2 mL of solution A to 10 mL with *chloroform*. For solution (2) transfer 2 mL of solution A to a 15 mL glass tube with a ground-glass stopper, add 10 mL of *saturated methanolic potassium hydrogen carbonate solution* and immediately pass a current of *nitrogen* briskly through the solution for 2 minutes. Stopper the tube, heat in a water bath at 45° protected from light for 2.5 hours and allow to cool. For solution (3) dissolve 25 mg of *fluocinonide BPCRS* in 5 mL of *methanol* (solution B); dilute 2 mL of solution B to 10 mL with *chloroform*. Prepare solution (4) in the same manner as solution (2) but use 2 mL of solution B in place of 2 mL of solution A. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The principal spots in each of the chromatograms obtained with solutions (1) and (2) are similar in position and size to those in the chromatograms obtained with solutions (3) and (4), respectively.

TESTS

Specific optical rotation

In a 1.0% w/v solution in *chloroform*, +81 to +89, calculated with reference to the dried substance, Appendix V F.

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the precoated plate and the mobile phase specified in test B for Identification. Apply separately to the plate 5 µL of each of four solutions in *chloroform* containing (1) 0.50% w/v of the substance being examined, (2) 0.010% w/v of the substance being examined, (3) 0.0050% w/v of the substance being examined and (4) 0.010% w/v of *fluocinolone acetonide BPCRS*. After removal of the plate, allow it to dry in air, heat the plate at 105° for 10 minutes, cool and spray with *alkaline tetrazolium blue solution*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (2%) and not more than one such spot is more intense than the spot in the chromatogram obtained with solution (3) (1%). The test is not valid unless the principal spot in the chromatogram obtained with solution (2) has an R_f value relative to the spot in the chromatogram obtained with solution (4) of at least 1.5.

Loss on drying

When dried at 100° to 105° for 3 hours, loses not more than 1.0% of its weight. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using two solutions in *methanol* containing (1) 0.012% w/v of the substance being examined and (2) 0.012% w/v of *fluocinonide BPCRS*.

The chromatographic procedure may be carried out using (a) a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable), (b) as the mobile phase with a flow rate of 1 mL per minute a mixture of 1 volume of *glacial acetic acid*, 450 volumes of *acetonitrile* and 550 volumes of *water* and (c) a detection wavelength of 238 nm.

Calculate the content of $C_{26}H_{32}F_2O_7$ using the declared content of $C_{26}H_{32}F_2O_7$ in *fluocinonide BPCRS*.

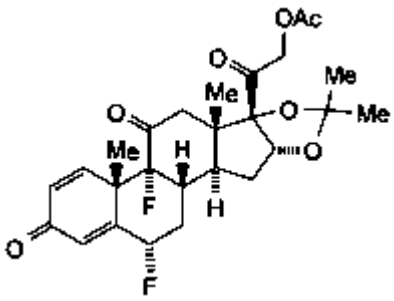
STORAGE

Fluocinonide should be protected from light.

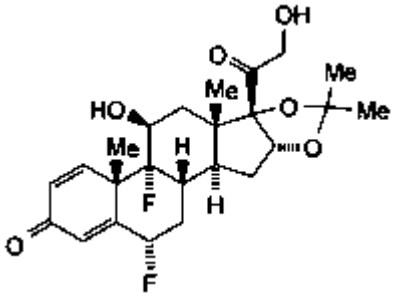
www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES



A. 6α,9α-difluoro-16α,17α-isopropylidene-3,11,20-trioxopregna-1,4-dien-21-yl acetate,



B. 6α,9α-difluoro-11β,21-dihydroxy-16α,17α-isopropylidenepregna-1,4-diene-3,20dione.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluocinonide Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluocinonide Cream contains Fluocinonide in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of fluocinonide, $C_{26}H_{32}F_2O_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the cream containing 2.5 mg of Fluocinonide in 25 mL of *methanol (80%)*, add 50 mL of *ether* and shake vigorously to produce a clear, homogeneous solution. Add 15 mL of *water*, shake and transfer the lower layer to a second separating funnel. Add 100 mL of *water*, extract with 10 mL of *chloroform*, filter the chloroform layer through filter paper and evaporate to a volume of about 1 mL in a current of air on a water bath.

(2) 0.1% w/v of *fluocinonide BPCRS* in a mixture of 1 volume of *methanol* and 9 volumes of *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

12 volumes of *water*, 80 volumes of *methanol*, 150 volumes of *ether* and 770 volumes of *dichloromethane*. Mix the water and the methanol before adding to the remaining solvents of the mobile phase.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the cream containing 1.5 mg of Fluocinonide in 20 mL of *methanol (80%)*, warming gently over a water bath if necessary. Add 50 mL of *2,2,4-trimethylpentane*, shake for 2 minutes and transfer the lower aqueous methanol layer to a 50-mL flask. Repeat the extraction with a further 20 mL of *methanol (80%)*. Dilute the combined extracts to volume with the same solvent.

(2) 0.003% w/v of *fluocinonide BPCRS* in *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.1 volume of *glacial acetic acid*, 45 volumes of *acetonitrile* and 55 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{32}F_2O_7$ in the cream using the declared content of $C_{26}H_{32}F_2O_7$ in *fluocinonide BPCRS*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluocinonide Ointment

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluocinonide Ointment contains Fluocinonide in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of fluocinonide, $C_{26}H_{32}F_2O_7$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the ointment containing 2 mg of fluocinonide in 20 mL of *methanol (80%)* in a 100-mL separating funnel containing 50 mL of *2,2,4-trimethylpentane*. Warm the contents over a water bath and shake gently. Allow the layers to separate and transfer the lower layer to a 250-mL separating funnel containing 100 mL of *water*. Add 10 mL of *chloroform* and shake for 3 minutes. Allow the layers to separate, evaporate the lower layer to dryness on a water bath in a current of air and dissolve the residue in 1 mL of *chloroform*.

(2) 0.2% w/v of *fluocinonide BPCRS* in *chloroform*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* F_{254}.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air until the solvent has evaporated. Heat at 105° for 5 minutes and spray while hot with *alkaline tetrazolium blue solution*.

MOBILE PHASE

12 volumes of *water*, 80 volumes of *methanol*, 150 volumes of *ether* and 770 volumes of *dichloromethane*. Mix the water and the methanol before adding to the remaining components of the mobile phase.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing 1.5 mg of fluocinonide in 20 mL of *methanol (80%)* in a 100-mL separating funnel containing 50 mL of *2,2,4-tri-methylpentane*. Warm the contents over a water bath and shake gently for 2 minutes. Allow the layers to separate and transfer the lower layer to a 50 mL flask. Repeat the extraction with a further 20 mL of *methanol (80%)*. Dilute the combined extracts to 50 mL with the same solvent.

(2) 0.003% w/v of *fluocinonide BPCRS* in *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.1 volume of *glacial acetic acid*, 45 volumes of *acetonitrile* and 55 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{26}H_{32}F_2O_7$ in the ointment using the declared content of $C_{26}H_{32}F_2O_7$ in *fluocinonide BPCRS*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

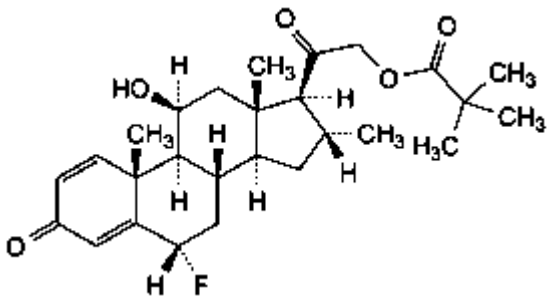
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluocortolone Pivalate

General Notices

(Ph. Eur. monograph 1212)



$C_{27}H_{37}FO_5$ 460.6 *29205-06-9*

Action and use

Glucocorticoid.

Preparation

Fluocortolone Cream

Ph Eur

DEFINITION

6α-Fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate.

Content

96.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

https://thuocngocanh.com/

IDENTIFICATION

First identification: A, B.

Second identification: C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *fluocortolone pivalate for ID and assay CRS*.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with test solution (b) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (c).

C. Thin-layer chromatography (2.2.27).

Solvent mixture *methanol R*, *methylene chloride R* (10:90 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve 20 mg of *fluocortolone pivalate for ID and assay CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (b) Dissolve 10 mg of *norethisterone CRS* in reference solution (a) and dilute to 10 mL with reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase Add a mixture of 1.2 volumes of *water R* and 8 volumes of *methanol R* to a mixture of 15 volumes of *ether R* and 77 volumes of *methylene chloride R*.

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

Detection B Spray with *alcoholic solution of sulfuric acid R*, heat at 120 °C for 10 min or until the spots appear, then allow to cool; examine in daylight and in ultraviolet light at 365 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

www.webofpharma.com

https://thuocngocanh.com/

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter and add to the filtrate a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Specific optical rotation (*2.2.7*)

+ 105 to + 110 (dried substance).

Dissolve 0.25 g in *methylene chloride R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in *acetonitrile R* and dilute to 25.0 mL with the same solvent.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in a mixture of 50.0 mL of *acetonitrile R* and 50.0 mL of *water R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 2 mg of *fluocortolone pivalate for system suitability CRS* (containing impurities C, D, E and F) in 2 mL of *acetonitrile R*.

Reference solution (c) Dissolve 25.0 mg of *fluocortolone pivalate for ID and assay CRS* in a mixture of 50.0 mL of *acetonitrile R* and 50.0 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *methanol R1*, *acetonitrile for chromatography R*, *water for chromatography R* (25:30:32 *V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 243 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time Twice the retention time of fluocortolone pivalate.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *fluocortolone pivalate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C, D, E and F.

Relative retention With reference to fluocortolone pivalate (retention time = about 21 min): impurity C = about 0.9; impurity D = about 1.1; impurity E = about 1.4; impurity F = about 1.6.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to fluocortolone pivalate and impurity D.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 1.4; impurity F = 1.3;

— for each impurity, use the concentration of fluocortolone pivalate in reference solution (a).

Limits:

— *impurities C, D*: for each impurity, maximum 1.0 per cent;

— *impurity E*: maximum 0.2 per cent;

— *impurity F*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Mobile phase *methanol R1*, *acetonitrile for chromatography R*, *water for chromatography R* (25:40:32 *V/V/V*).

Injection 10 µL of test solution (b) and reference solutions (b) and (c).

Run time 1.5 times the retention time of fluocortolone pivalate.

Relative retention With reference to fluocortolone pivalate (retention time = about 11 min): impurity D = about 1.1.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to fluocortolone pivalate and impurity D.

Calculate the percentage content of $C_{27}H_{37}FO_5$ taking into account the assigned content of *fluocortolone pivalate for ID and assay CRS*.

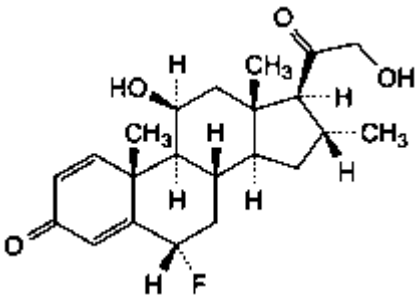
STORAGE

Protected from light.

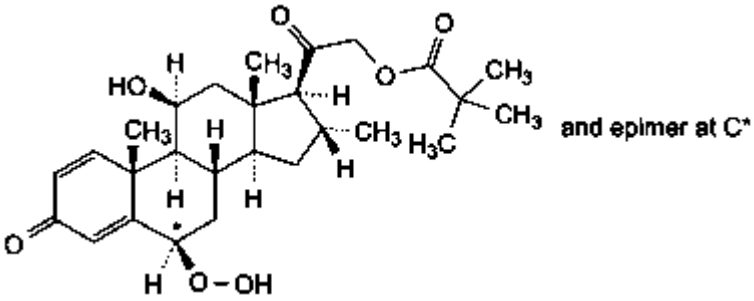
IMPURITIES

Specified impurities *C, D, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B.*



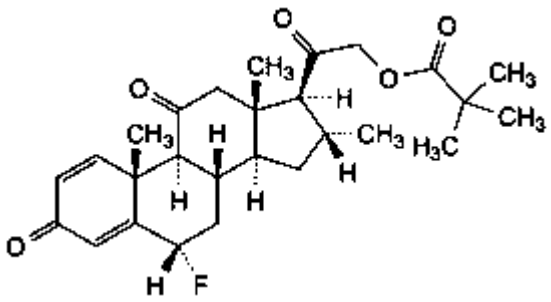
A. 6α-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione (fluocortolone),



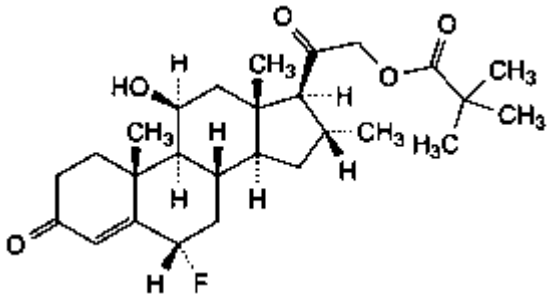
B. 6αβ-hydroperoxy-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate,

www.webofpharma.com

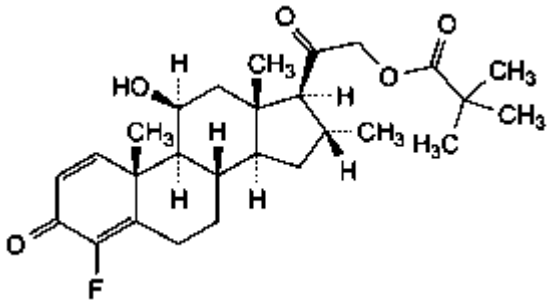
https://thuocngocanh.com/



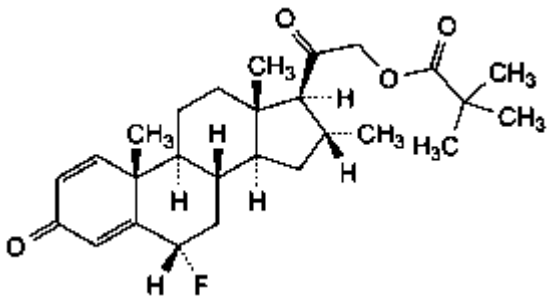
C. 6α-fluoro-16α-methyl-3,11,20-trioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate,



D. 6α-fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregn-4-en-21-yl 2,2-dimethylpropanoate,



E. 4-fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate,



F. 6α-fluoro-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

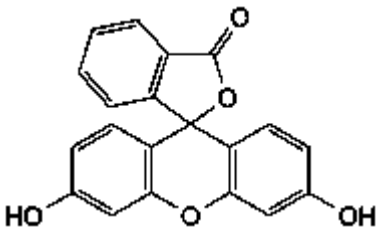
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorescein

General Notices

(Ph. Eur. monograph 2348)



$C_{20}H_{12}O_5$ 332.3 *2321-07-5*

Action and use

Detection of corneal lesions, retinal angiography and pancreatic function testing.

Ph Eur

DEFINITION

3′,6′-Dihydroxy-3*H*-spiro[isobenzofuran-1,9′-xanthen]-3-one.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Orange-red, fine powder.

Solubility

Practically insoluble in water, soluble in hot ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *fluorescein CRS*.

Dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol (96 per cent) R*, evaporate to dryness and record the spectra using the residues.

B. Dilute 0.1 mL of solution S (see Tests) to 10 mL with *water R*. The solution shows a yellowish-green fluorescence. The fluorescence disappears on addition of 0.1 mL of *dilute hydrochloric acid R* and reappears on addition of 0.2 mL of *dilute sodium hydroxide solution R*.

C. The absorption by a piece of filter paper of 0.05 mL of the solution prepared for identification B (before the addition of *dilute hydrochloric acid R*) colours the paper yellow. On exposing the moist paper to bromine vapour for 1 min and then to ammonia vapour, the colour becomes deep pink.

D. Suspend 0.5 g in 50 mL of *water R* and shake for 10 min. The substance does not completely dissolve.

TESTS

Solution S

Suspend 1.0 g in 35.0 mL of *water R* and add dropwise with shaking 4.5 mL of *1 M sodium hydroxide*. Adjust to pH 8.5-9.0 with *1 M sodium hydroxide* and dilute to 50.0 mL with *water R* to obtain a clear solution.

Appearance of solution

Solution S is clear (2.2.1) and orange-red with yellowish-green fluorescence.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile for chromatography R*, mobile phase A (30:70 *V/V*).

Test solution (a) Disperse 50.0 mg of the substance to be examined in 15.0 mL of *ethanol (96 per cent) R*. Sonicate and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 250.0 mL with the solvent mixture.

Reference solution (a) Disperse 50.0 mg of *fluorescein CRS* in 15.0 mL of *ethanol (96 per cent) R*. Sonicate and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 250.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *phthalic acid CRS* (impurity B) and 10.0 mg of *resorcinol CRS* (impurity A) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dilute 5.0 mL of test solution (b) to 20.0 mL with the solvent mixture.

Reference solution (d) Dilute 10.0 mL of reference solution (c) to 100.0 mL with the solvent mixture.

Reference solution (e) Dissolve the contents of a vial of *fluorescein impurity C CRS* in 1 mL of the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octylsilyl silica gel for chromatography R3 (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.610 g of potassium dihydrogen phosphate R in water for chromatography R, adjust to pH 2.0 with phosphoric acid R and dilute to 1000.0 mL with water for chromatography R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	85 → 20	15 → 80
20 - 29	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (b), (c), (d) and (e).

Identification of impurity C Use the chromatogram obtained with reference solution (e) to identify the peak due to impurity C.

Relative retention With reference to fluorescein (retention time = about 15 min): impurity A = about 0.42; impurity B = about 0.48; impurity C = about 0.86.

System suitability Reference solution (b):

— resolution: minimum 2.0 between the peaks due to impurities A and B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.9;

— *impurity C*: not more than 1.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent);

— *impurities A, B*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *sum of impurities other than A, B and C*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent).

Chlorides (2.4.4)

Maximum 0.25 per cent.

To 10.0 mL of solution S add 90.0 mL of *water R* and 3.0 mL of *dilute nitric acid R*, wait for at least 30 min and filter. Dilute 10.0 mL of the filtrate to 15.0 mL with *water R*.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

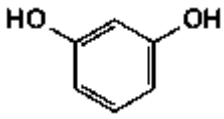
Calculate the percentage content of $C_{20}H_{12}O_5$ taking into account the assigned content of *fluorescein CRS*.

STORAGE

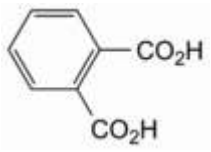
Protected from light.

IMPURITIES

Specified impurities *A, B, C.*



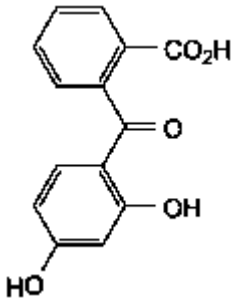
A. benzene-1,3-diol (resorcinol),



B. benzene-1,2-dicarboxylic acid (phthalic acid),

www.webofpharma.com

https://thuocngocanh.com/



C. 2-(2,4-dihydroxybenzoyl)benzoic acid.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorescein Eye Drops

General Notices

Action and use

Detection of corneal lesions, retinal angiography and pancreatic function testing.

DEFINITION

Fluorescein Eye Drops are a sterile solution of Fluorescein Sodium in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of fluorescein sodium, $C_{20}H_{10}Na_2O_5$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Evaporate a volume containing 20 mg of fluorescein sodium and dry at 105° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fluorescein sodium *(RS 151)*.

B. The eye drops are strongly fluorescent, even in extreme dilution; the fluorescence disappears when the solution is made acidic and reappears when it is made alkaline.

C. Dilute with *water* to produce a solution containing 0.05% w/v of fluorescein sodium. One drop of the solution, absorbed by a piece of filter paper, colours the paper yellow. On exposing the moist paper to bromine vapour for 1 minute and then to ammonia vapour the yellow colour becomes deep pink.

TESTS

Acidity or alkalinity

pH, 7.0 to 9.0, Appendix V L.

Chloroform-soluble matter

To a volume containing 0.1 g of fluorescein sodium add 1 mL of 2M *sodium hydroxide*, extract with 10 mL of *chloroform* and dry the chloroform layer with *anhydrous sodium sulfate*. The *absorbance* of the resulting solution at 480 nm is not more than 0.05, Appendix II B, using *chloroform* in the reference cell.

Related substances and resorcinol

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dilute the eye drops with 0.1M *methanolic hydrochloric acid* to contain 0.5% w/v of fluorescein sodium.

(2) Add to a volume of the eye drops containing 25 mg of fluorescein sodium 2 mL of *phosphate buffer pH 8.0*, 3 mL of *water* and 2.5 g of *sodium chloride*, shake to dissolve the sodium chloride and extract with two 25-mL quantities of *peroxide-free ether*. Dry the combined extracts over *anhydrous sodium sulfate*, evaporate to dryness under reduced pressure and dissolve the residue in 1 mL of 0.1M *methanolic hydrochloric acid*.

(3) Dilute 1 volume of solution (1) to 100 volumes with 0.1M *methanolic hydrochloric acid*.

(4) Dilute 2 volumes of solution (3) to 5 volumes with 0.1M *methanolic hydrochloric acid*.

(5) 0.0125% w/v of *resorcinol* in 0.1M *methanolic hydrochloric acid*.

(6) Mix 5 volumes of a 0.025% w/v solution of *resorcinol* in 0.1M *methanolic hydrochloric acid* with 2 volumes of solution (1) and add sufficient *methanol* to produce 10 mL.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel 60 F_{254} precoated plate (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of solution (1) and 5 µL of solutions (2) to (6).

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, expose the plate to iodine vapour for 30 minutes and examine in daylight and under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (6) shows two clearly separated spots in daylight.

LIMITS

In the chromatogram obtained with solution (1), under *ultraviolet light (254 nm)*:

any *secondary spot*, other than any spot corresponding to resorcinol, is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (4) (0.2%).

In the chromatogram obtained with solution (2), in daylight:

any spot corresponding to resorcinol in the chromatogram obtained with solution (2) is not more intense than the spot in the chromatogram obtained with solution (5) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute the eye drops with the mobile phase to produce a solution containing 0.005% w/v of fluorescein sodium.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dissolve 55 mg of *diacetylfluorescein BPCRS* in a mixture of 5 mL of *ethanol (96%)* and 1 mL of 2.5M *sodium hydroxide*, heat on a water bath for 20 minutes, mixing frequently, cool and add sufficient *water* to produce 50 mL. Dilute 5 volumes of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 ml per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *triethylamine*, 400 volumes of *acetonitrile* and 595 volumes of *water*, adjust the pH to 3.0 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{10}Na_2O_5$ in the eye drops using the declared content of anhydrous diacetylfluorescein in *diacetylfluorescein BPCRS*. Each mg of anhydrous diacetylfluorescein is equivalent to 0.9037 mg of $C_{20}H_{10}Na_2O_5$.

STORAGE

Fluorescein Eye Drops should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorescein Injection

General Notices

Action and use

Detection of corneal lesions, retinal angiography and pancreatic function testing.

DEFINITION

Fluorescein Injection is a sterile solution of Fluorescein Sodium in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of fluorescein sodium, $C_{20}H_{10}Na_2O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Evaporate 1 mL to dryness on a water bath and dry the residue at 105° for 30 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fluorescein sodium *(RS 151)*.

B. The injection is strongly fluorescent, even in extreme dilution; the fluorescence disappears when the solution is made acidic and reappears when it is made alkaline.

C. Dilute with *water* to produce a solution containing 0.05% w/v of fluorescein sodium. One drop of the solution, absorbed by a piece of filter paper, colours the paper yellow. On exposing the moist paper to bromine vapour for 1 minute and then to ammonia vapour the yellow colour becomes deep pink.

TESTS

Alkalinity

pH, 8.0 to 9.8, Appendix V L.

Chloroform-soluble matter

Dilute the injection with *water*, if necessary, to produce a solution containing 1% w/v of fluorescein sodium. To 20 mL add 5 mL of 1M *sodium hydroxide*, dilute to 50 mL with *water*, extract with 10 mL of *chloroform* and dry the chloroform layer over *anhydrous sodium sulfate*. The *absorbance* of the resulting solution at 480 nm is not more than 0.10, Appendix II B, using *chloroform* in the reference cell.

Related substances and resorcinol

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dilute the injection with 0.1M *methanolic hydrochloric acid* to produce a solution containing 1.0% w/v of fluorescein sodium.

(2) Dilute a quantity of the injection containing 250 mg of fluorescein sodium to 5 mL with *water*, add 2 mL of *phosphate buffer pH 8.0*, 3 mL of *water* and 2.5 g of *sodium chloride*, shake to dissolve the sodium chloride and extract with two 25-mL quantities of *peroxide-free ether*. Dry the combined extracts over *anhydrous sodium sulfate*, evaporate to dryness under reduced pressure and dissolve the residue in 10 mL of 0.1M *methanolic hydrochloric acid*.

(3) Dilute 1 volume of solution (1) to 200 volumes with 0.1M *methanolic hydrochloric acid*.

(4) Dilute 2 volumes of solution (3) to 5 volumes with 0.1M *methanolic hydrochloric acid*.

(5) 0.0125% w/v of *resorcinol* in 0.1M *methanolic hydrochloric acid*.

(6) Mix 1 volume of solution (1) with 9 volumes of solution (5).

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel 60 F_{254} precoated plate (Merck plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, expose the plate to iodine vapour for 30 minutes and examine in daylight and under *ultraviolet light (254 nm)*.

MOBILE PHASE

10 volumes of *methanol* and 90 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (6) shows two clearly separated spots in daylight.

LIMITS

In the chromatogram obtained with solution (1), under ultraviolet light (254 nm):

any *secondary spot*, other than any spot corresponding to resorcinol, is not more intense than the spot in the chromatogram obtained with solution (3) (0.5%);

not more than one such spot is more intense than the spot in the chromatogram obtained with solution (4) (0.2%).

In the chromatogram obtained with solution (2), in daylight:

any spot corresponding to resorcinol in the chromatogram obtained with solution (2) is not more intense than the spot in the chromatogram obtained with solution (5) (0.5%).

On examination in daylight, any spot corresponding to resorcinol in the chromatogram obtained with solution (2) is not more intense than the spot in the chromatogram obtained with solution (5) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dilute the injection with *water*, if necessary, to produce a solution containing 1.0% w/v of fluorescein sodium and dilute 1 volume of this solution to 200 volumes with the mobile phase.

(2) Dissolve 55 mg of *diacetylfluorescein BPCRS* in a mixture of 5 mL of *ethanol (96%)* and 1 mL of 2.5M *sodium hydroxide*, heat on a water bath for 20 minutes, mixing frequently, cool and add sufficient *water* to produce 50 mL. Dilute 5 volumes of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 2 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 ml per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *triethylamine*, 400 volumes of *acetonitrile* and 595 volumes of *water*, adjust the pH to 3.0 with *orthophosphoric acid*

DETERMINATION OF CONTENT

Calculate the content of $C_{20}H_{10}Na_2O_5$ in the eye drops using the declared content of anhydrous diacetylfluorescein in *diacetylfluorescein BPCRS*. Each mg of anhydrous diacetylfluorescein is equivalent to 0.9037 mg of $C_{20}H_{10}Na_2O_5$.

STORAGE

Fluorescein Injection should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

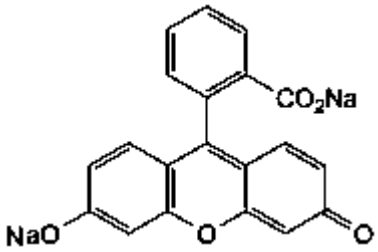
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorescein Sodium

General Notices

Soluble Fluorescein

(Ph. Eur. monograph 1213)



$C_{20}H_{10}Na_2O_5$ 376.3 *518-47-8*

Action and use

Detection of corneal lesions, retinal angiography and pancreatic function testing.

Preparations

Fluorescein Eye Drops

Fluorescein Injection

Ph Eur

DEFINITION

Disodium 2-(6-oxido-3-oxo-3*H*-xanthen-9-yl)benzoate.

Content

95.0 per cent to 103.0 per cent (dried substance).

CHARACTERS

Appearance

Orange-red, fine powder, hygroscopic.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in hexane and in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Dilute 0.1 mL of solution S (see Tests) to 10 mL with *water R*. The solution shows yellowish-green fluorescence. The fluorescence disappears on addition of 0.1 mL of *dilute hydrochloric acid R* and reappears on addition of 0.2 mL of *dilute sodium hydroxide solution R*.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Comparison *Ph. Eur. reference spectrum of fluorescein sodium*.

C. The absorption by a piece of filter paper of 0.05 mL of the solution prepared for identification A (before the addition of *dilute hydrochloric acid R*) colours the paper yellow. On exposing the moist paper to bromine vapour for 1 min and then to ammonia vapour, the colour becomes deep pink.

D. Ignite 0.1 g in a porcelain crucible. Dissolve the residue in 5 mL of *water R* and filter. 2 mL of the filtrate gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and orange-yellow with yellowish-green fluorescence.

pH (*2.2.3*)

7.0 to 9.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 0.100 g of the substance to be examined in a mixture of 30 volumes of *acetonitrile R* and 70 volumes of mobile phase A and dilute to 100.0 mL with the same mixture of solvents.

Test solution (b) Dilute 5.0 mL of test solution (a) to 250.0 mL with a mixture of 30 volumes of *acetonitrile R* and 70 volumes of mobile phase A.

Reference solution (a) Dissolve 55.0 mg of *diacetylfluorescein CRS* in a mixture of 1 mL of *2.5 M sodium hydroxide* and 5 mL of *ethanol (96 per cent) R*, heat on a water-bath for 20 min mixing frequently, cool and dilute to 50.0 mL with *water R*. Dilute 5.0 mL of the solution to

www.webofpharma.com

https://thuocngocanh.com/

250.0 mL with a mixture of 30 volumes of *acetonitrile R* and 70 volumes of mobile phase A.

Reference solution (b) Dissolve 10.0 mg of *phthalic acid R* (impurity B) and 10.0 mg of *resorcinol R* (impurity A) in a mixture of 30 volumes of *acetonitrile R* and 70 volumes of mobile phase A and dilute to 100.0 mL with the same mixture of solvents. Dilute 5.0 mL of the solution to 100.0 mL with a mixture of 30 volumes of *acetonitrile R* and 70 volumes of mobile phase A.

Reference solution (c) Dilute 5.0 mL of test solution (b) to 20.0 mL with a mixture of 30 volumes of *acetonitrile R* and 70 volumes of mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.610 g of *potassium dihydrogen phosphate R* in *water R* and dilute to 1000 mL with the same solvent; adjust to pH 2.0 with *phosphoric acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	85 → 20	15 → 80
20 - 29	20	80
29 - 30	20 → 85	80 → 15
30 - 35	85	15

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL of test solution (a) and reference solutions (b) and (c).

Relative retention With reference to fluorescein (retention time = about 15 min): impurity A = about 0.4; impurity B = about 0.5; impurity C = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity A and impurity B.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.6;

— *impurities A, B*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *sum of impurities other than A, B, C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Chlorides (2.4.4)

Maximum 0.25 per cent.

To 10 mL of solution S add 90 mL of *water R* and 1 mL of *dilute nitric acid R*, wait for at least 10 min and filter. Dilute 10 mL of the filtrate to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 1.0 per cent.

To 5 mL of solution S add 90 mL of *distilled water R*, 2.5 mL of *dilute hydrochloric acid R* and dilute to 100 mL with *distilled water R*. Filter.

Zinc

Dilute 5 mL of solution S to 10 mL with *water R*. Add 2 mL of *hydrochloric acid R1*, filter and add 0.1 mL of *potassium ferrocyanide solution R*. No turbidity or precipitate is formed immediately.

Loss on drying (2.2.32)

Maximum 10.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{20}H_{10}Na_2O_5$ using the chromatogram obtained with reference solution (a) and the declared content of *diacetylfluorescein CRS*.

1 mg of *diacetylfluorescein CRS* is equivalent to 0.9037 mg of $C_{20}H_{10}Na_2O_5$.

www.webofpharma.com

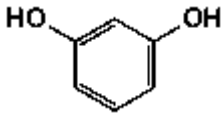
https://thuocngocanh.com/

STORAGE

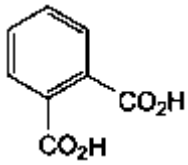
In an airtight container, protected from light.

IMPURITIES

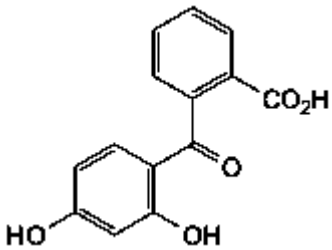
Specified impurities *A, B, C.*



A. benzene-1,3-diol (resorcinol),



B. benzene-1,2-dicarboxylic acid (phthalic acid),



C. 2-(2,4-dihydroxybenzoyl)benzoic acid.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

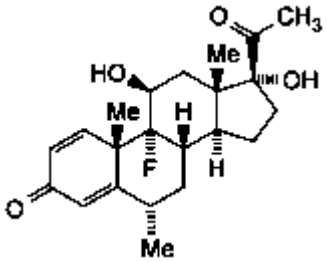
https://thuocngocanh.com/

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorometholone

General Notices



$C_{22}H_{29}FO_4$ 376.5 *426-13-1*

Action and use

Glucocorticoid.

Preparation

Fluorometholone Eye Drops

DEFINITION

Fluorometholone is 9α-fluoro-11β,17α-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione. It contains not less than 97.0% and not more than 103.0% of $C_{22}H_{29}FO_4$, calculated with reference to the dried substance.

CHARACTERISTICS

A white to yellowish white, crystalline powder. It melts at about 280°, with decomposition.

Practically insoluble in *water*; slightly soluble in *absolute ethanol* and in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of fluorometholone *(RS 152)*.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Specific optical rotation

www.webofpharma.com

https://thuocngocanh.com/

In a 1% w/v solution in *pyridine*, +52 to +60, Appendix V F, calculated with reference to the dried substance.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

(1) 0.010% w/v of the substance being examined.

(2) 0.00005% w/v of the substance being examined.

(3) 0.00005% w/v each of *deltamedrane BPCRS* and *fluorometholone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of *water* and 60 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to deltamedrane and fluorometholone is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Loss on drying

When dried at 60° at a pressure not exceeding 0.7 kPa for 3 hours, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.1%, Appendix IX A.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

(1) 0.005% w/v of the substance being examined.

(2) 0.005% w/v of *fluorometholone BPCRS*.

(3) 0.00005% w/v each of *deltamedrane BPCRS* and *fluorometholone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

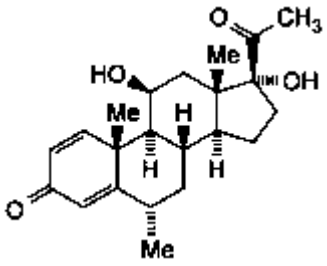
SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to deltamedrane and fluorometholone is at least 1.5.

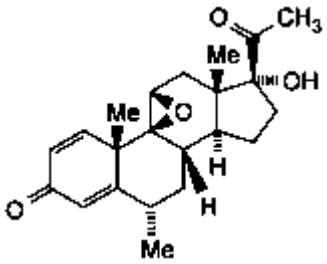
DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_4$ from the chromatograms obtained and using the declared content of $C_{22}H_{29}FO_4$ in *fluorometholone BPCRS*.

IMPURITIES



A. 11β,17α-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione *(deltamedrane)*,



B. 9β,11β-epoxy-17α-hydroxy-6α-methylpregna-1,4-diene-3,20-dione *(epoxymedradiene)*.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorometholone Eye Drops

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluorometholone Eye Drops are a sterile suspension of Fluorometholone in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of fluorometholone, $C_{22}H_{29}FO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the eye drops containing 5 mg of Fluorometholone with 20 mL of *acetone*, filter and evaporate the filtrate to dryness. Dissolve the residue in 10 mL of *acetone*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fluorometholone *(RS 152)*.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the eye drops containing 1 mg of Fluorometholone to 10 mL with a mixture of equal volumes of *methanol* and *water*.

(2) Dilute 1 volume of solution (1) to 20 volumes with *methanol* and further dilute 1 volume to 10 volumes with *methanol*.

(3) 0.00005% w/v each of *deltamedrane BPCRS* and *fluorometholone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (µBondapak C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of *water* and 60 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to deltamedrane and fluorometholone is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix the eye drops thoroughly and dilute a quantity containing 1 mg of Fluorometholone to 25 mL with a mixture of equal volumes of *methanol* and *water*.

(2) Dilute 4 mL of a 0.05% w/v solution of *fluorometholone BPCRS* in *methanol* to 50 mL with a mixture of equal volumes of *methanol* and *water*.

(3) 0.00005% w/v each of *deltamedrane BPCRS* and *fluorometholone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to deltamedrane and fluorometholone is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{29}FO_4$ in the eye drops using the declared content of $C_{22}H_{29}FO_4$ in *fluorometholone BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

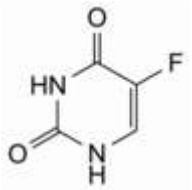
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorouracil

General Notices

(Ph. Eur. monograph 0611)



$C_4H_3FN_2O_2$ 130.1 *51-21-8*

Action and use

Pyrimidine analogue; cytotoxic.

Preparations

Fluorouracil Cream

Fluorouracil Injection

Ph Eur

DEFINITION

5-Fluoropyrimidine-2,4(1*H*,3*H*)-dione.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *fluorouracil CRS*.

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution BY_7 or Y_7 (2.2.2, *Method II*).

pH (2.2.3)

4.5 to 5.0 for solution S.

Impurities F and G

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.10 g of the substance to be examined in a mixture of equal volumes of *methanol R* and *water R* and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 5.0 mg of *fluorouracil impurity F CRS* in a mixture of equal volumes of *methanol R* and *water R* and dilute to 200.0 mL with the same mixture of solvents.

Reference solution (b) Dissolve 20.0 mg of *urea R* (impurity G) in *methanol R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *methanol R*, *water R*, *ethyl acetate R* (15:15:70 *V/V/V*).

Application 10 µL.

Development Over a path of 2/3 of the plate.

Drying In air.

Detection:

— *impurity F*: examine in ultraviolet light at 254 nm;

— *impurity G*: spray with a mixture of 200 mL of a 10 g/L solution of *dimethylaminobenzaldehyde R* in *anhydrous ethanol R* and 20 mL of *hydrochloric acid R*; dry in an oven at 80 °C for 3-4 min, then examine in daylight (impurity G produces a yellow spot and fluorouracil is not detected by the spray).

www.webofpharma.com

https://thuocngocanh.com/

System suitability The chromatogram shows 2 clearly separated spots after both detections.

Limits:

— *impurity F*: any spot due to impurity F is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.25 per cent);

— *impurity G*: any spot due to impurity G is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light*.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *fluorouracil impurity C CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5.0 mg of *fluorouracil impurity A CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 5.0 mg of *fluorouracil impurity B CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (e) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (f) To 1 mL of reference solution (a) add 1 mL of the test solution and dilute to 10 mL with the mobile phase.

Reference solution (g) Dissolve the contents of a vial of *fluorouracil impurity mixture CRS* (containing impurities D and E) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 6.805 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 5.7 ± 0.1 with a 5 M potassium hydroxide solution prepared from *potassium hydroxide R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 266 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL.

Run time 3 times the retention time of fluorouracil.

Identification of impurities Use the chromatogram supplied with *fluorouracil impurity mixture CRS* and the chromatogram obtained with reference solution (g) to identify the peaks due to impurities D and E.

Relative retention With reference to fluorouracil (retention time = about 6 min): impurity A = about 0.5; impurity B = about 0.7; impurity C = about 0.9; impurity D = about 1.6; impurity E = about 1.9.

System suitability Reference solution (f):

— *resolution*: minimum 2 between the peaks due to impurity C and fluorouracil.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.5; impurity E = 1.3;

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *impurities D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.100 g in 80 mL of *dimethylformamide R*, warming gently. Cool and titrate with 0.1 M tetrabutylammonium hydroxide, using 0.25 mL of a 10 g/L solution of *thymol blue R* in *dimethylformamide R* as indicator. Carry out a blank titration.

www.webofpharma.com

https://thuocngocanh.com/

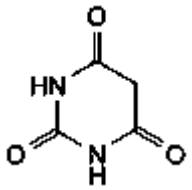
1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 13.01 mg of $C_4H_3FN_2O_2$.

STORAGE

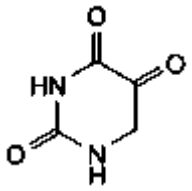
Protected from light.

IMPURITIES

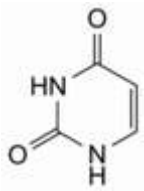
Specified impurities *A, B, C, D, E, F, G.*



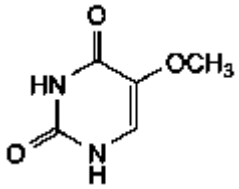
A. pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (barbituric acid),



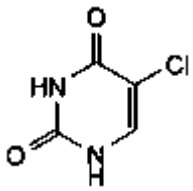
B. dihydropyrimidine-2,4,5(3*H*)-trione (isobarbituric acid or 5-hydroxyuracil),



C. pyrimidine-2,4(1*H*,3*H*)-dione (uracil),



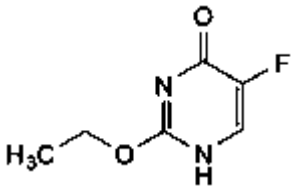
D. 5-methoxypyrimidine-2,4(1*H*,3*H*)-dione (5-methoxyuracil),



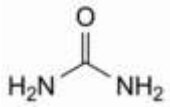
E. 5-chloropyrimidine-2,4(1*H*,3*H*)-dione (5-chlorouracil),

www.webofpharma.com

https://thuocngocanh.com/



F. 2-ethoxy-5-fluoropyrimidin-4(1*H*)-one (2-ethoxy-5-fluorouracil),



G. carbamide (urea).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorouracil Cream

General Notices

Action and use

Pyrimidine analogue; cytotoxic.

DEFINITION

Fluorouracil Cream contains Fluorouracil in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of fluorouracil, $C_4H_3FN_2O_2$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Dry a quantity containing 50 mg of Fluorouracil at a pressure not exceeding 0.7 kPa, mix with 100 mL of *ether*, decant, wash the white, crystalline residue with 50 mL of *ether* and dry in air. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fluorouracil *(RS 153)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits a maximum only at 266 nm.

TESTS

5-Hydroxyuracil

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the cream containing 0.10 g of Fluorouracil with 10 mL of *water* for 5 minutes, add 10 mL of *ethanol (96%)*, mix and filter through glass-fibre paper.

(2) 0.00125% w/v of *5-hydroxyuracil* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with a freshly prepared 0.5% w/v solution of *fast blue B salt* and then with 0.1M *sodium hydroxide*.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

10 volumes of *water* , 40 volumes of *acetone* and 70 volumes of *ethyl acetate*.

LIMITS

Any spot corresponding to 5-hydroxyuracil in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Urea

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the cream containing 0.10 g of Fluorouracil with 10 mL of *water* for 5 minutes, add 10 mL of *ethanol (96%)*, mix and filter through glass-fibre paper.
(2) 0.0050% w/v of *urea* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 20 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, allow it to dry in air, spray with a mixture of 10 volumes of a 1% w/v solution of *4-dimethylaminobenzaldehyde* in *ethanol (96%)* and 1 volume of *hydrochloric acid* and heat at 100° until maximum intensity of the spots is obtained.

MOBILE PHASE

10 volumes of *water*, 40 volumes of *acetone* and 70 volumes of *ethyl acetate*.

LIMITS

Any spot corresponding to urea in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

ASSAY

To a quantity containing 50 mg of Fluorouracil add 50 mL of 0.1M *hydrochloric acid* and shake for 5 minutes. Extract with three 25-mL quantities of *chloroform*, discard the chloroform, dilute the aqueous solution to 250 mL with 0.1M *hydrochloric acid* and filter (Whatman No. 42 paper is suitable). Dilute 5 mL to 100 mL with 0.1M *hydrochloric acid* and measure the *absorbance* of the resulting solution at the maximum at 266 nm, Appendix II B. Calculate the content of $C_4H_3FN_2O_2$ taking 552 as the value of A(1%, 1 cm) at the maximum at 266 nm.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluorouracil Injection

General Notices

Action and use

Pyrimidine analogue; cytotoxic.

DEFINITION

Fluorouracil Injection is a sterile solution in Water for Injections of fluorouracil sodium, prepared by the interaction of Fluorouracil and Sodium Hydroxide.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of fluorouracil, $C_4H_3FN_2O_2$

90.0 to 110.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. Carefully acidify a volume containing the equivalent of 0.1 g of fluorouracil with *glacial acetic acid*, stir, cool and filter. Wash the precipitate with 1 mL of *water* and dry over *phosphorus pentoxide* at 80° at a pressure of 2 kPa for 4 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fluorouracil *(RS 153)*.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the solution obtained in the Assay exhibits a maximum only at 266 nm.

TESTS

Alkalinity

pH, 8.5 to 9.1, Appendix V L.

Urea

Carry out the method described under Related substances applying separately to the plate 20 µL of each of the following solutions. For solution (1) dilute a suitable quantity of the injection with *water* to produce a solution containing the equivalent of 0.50% w/v of fluorouracil. Solution (2) contains 0.020% w/v of *urea* in *water*. After removal of the plate, allow it to dry in air, spray with a mixture of 10 volumes of a 1% w/v solution of *4-dimethylaminobenzaldehyde* in *ethanol (96%)* and 1 volume of *hydrochloric acid* and heat at 100° until maximum

www.webofpharma.com

https://thuocngocanh.com/

intensity of the spots is obtained. Any spot corresponding to urea in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 70 volumes of *ethyl acetate*, 15 volumes of *methanol* and 15 volumes of *water* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) dilute a suitable quantity of the injection with *water* to produce a solution containing the equivalent of 2.0% w/v of fluorouracil. For solution (2) dilute 1 volume of solution (1) to 400 volumes with *methanol (50%)*. Solution (3) contains 0.0050% w/v of *5-hydroxyuracil* in *methanol (50%)*. After removal of the plate, allow it to dry in a current of air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2). Spray with a freshly prepared 0.5% w/v solution of *fast blue B salt* and then with 0.1M *sodium hydroxide*. Any spot corresponding to 5-hydroxyuracil in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (3). Disregard any spots with Rf values lower than 0.2.

ASSAY

To a volume containing the equivalent of 75 mg of fluorouracil add 20 mL of 1M *hydrochloric acid* and sufficient *water* to produce 200 mL. Dilute 3 mL to 100 mL with 0.1M *hydrochloric acid* and measure the *absorbance* of the resulting solution at the maximum at 266 nm, Appendix II B. Calculate the content of $C_4H_3FN_2O_2$ taking 552 as the value of A(1%,1 cm) at the maximum at 266 nm.

STORAGE

Fluorouracil Injection should be protected from light. It should not be refrigerated.

LABELLING

The strength is stated in terms of the equivalent amount of Fluorouracil in a suitable dose-volume.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluoxetine Capsules

General Notices

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

DEFINITION

Fluoxetine Capsules contain Fluoxetine Hydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of fluoxetine, $C_{17}H_{18}F_3NO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the contents of the capsules containing the equivalent of 20 mg of fluoxetine with 10 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fluoxetine hydrochloride *(RS 385)*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1. Prepare a mixture of 1 volume of *diethylamine* and 250 volumes of *acetonitrile*, mix well and adjust the pH to 3.5 with *orthophosphoric acid* (solution A); a white precipitate may form, keep the mixture well stirred.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of 20 mL of the medium and filter, discarding the first 5 mL of filtrate. Add to 5 mL of filtered medium 2 mL of solution A and mix well.

www.webofpharma.com

https://thuocngocanh.com/

(2) Add to 5 mL of a 0.0022% w/v solution of *fluoxetine hydrochloride BPCRS,* 2 mL of solution A and mix well.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Zorbax CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 226 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

2 volumes of *diethylamine*, 200 volumes of *acetonitrile* and 300 volumes of *water*, the mixture adjusted to pH 3.5 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{18}F_3NO$ in the medium from the chromatograms obtained using the declared content of $C_{17}H_{18}F_3NO,HCl$ in *fluoxetine hydrochloride BPCRS* and taking each mg of $C_{17}H_{18}F_3NO,HCl$ to be equivalent to 0.8944 mg of $C_{17}H_{18}F_3NO$.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the contents of the capsules containing the equivalent of 20 mg of fluoxetine in sufficient of the mobile phase to produce 10 mL, filter and use the filtrate, discarding the first 2 mL.

(2) 0.001% w/v of *fluoxetine hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (DuPont Zorbax SB-CN is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of the peak due to fluoxetine hydrochloride.

If necessary, adjust the composition of the mobile phase so that, in the chromatogram obtained with solution (2), the retention time of the peak due to fluoxetine is between 10 and 20 minutes.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of a solution containing 1 volume of *triethylamine* and 99 volumes of *water*, and adjusting the pH to 6.0 with *orthophosphoric acid*.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any *secondary peak* is not greater than half the area of the peak in the chromatogram obtained with solution (2) (0.25%);

the area of not more than two such peaks is greater than 0.2 times the area of the peak in the chromatogram obtained with solution (2) (0.1%);

and the sum of the areas of all the *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of 20 capsules containing the equivalent of 20 mg of fluoxetine in sufficient of the mobile phase to produce 200 mL, filter and use the filtrate, discarding the first 2 mL.
(2) 0.011% w/v of *fluoxetine hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (7.5 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (3.5 µm) (DuPont Zorbax RX-C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 227 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

33 volumes of a solution containing 0.3% w/v of *glacial acetic acid* and 0.64% w/v of *sodium pentanesulfonate*, adjusted to pH 5.0 with 5M *sodium hydroxide*, and 67 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{18}F_3NO$ in the capsules from the chromatograms obtained using the declared content of $C_{17}H_{18}F_3NO$,HCl in *fluoxetine hydrochloride BPCRS* and taking each mg of $C_{17}H_{18}F_3NO$,HCl to be equivalent to 0.8944 mg of $C_{17}H_{18}F_3NO$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of fluoxetine.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and B listed under Fluoxetine Hydrochloride.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

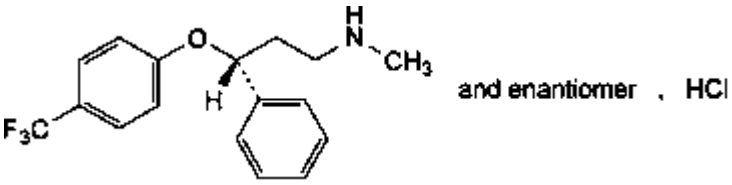
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluoxetine Hydrochloride

General Notices

(Ph. Eur. monograph 1104)



$C_{17}H_{19}ClF_3NO$ 345.8 *56296-78-7*

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

Preparations

Fluoxetine Capsules

Fluoxetine Oral Solution

Ph Eur

DEFINITION

(3*RS*)-*N*-Methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine hydrochloride.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in methanol, sparingly soluble in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *fluoxetine hydrochloride for ID and assay CRS*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 2.0 g in a mixture of 15 volumes of *water R* and 85 volumes of *methanol R*, then dilute to 100.0 mL with the same mixture of solvents.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

4.5 to 6.5.

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Optical rotation (2.2.7)

-0.05° to + 0.05°, determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *methanol R*, solution A (40:60 *V/V*).

Solution A Mix 12.5 mL of *triethylamine R* and about 900 mL of *water for chromatography R*, adjust to pH 6.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Test solution (a) Dissolve 0.500 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *fluoxetine hydrochloride for ID and assay CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *fluoxetine impurity A CRS* and 5.0 mg of *fluoxetine impurity B CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (d) Dissolve 2 mg of *fluoxetine impurity C CRS* in test solution (a) and dilute to 10 mL with test solution (a). Dilute 1 mL of the solution to 10 mL with test solution (a).

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.0 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *methanol R2*, solution A (20:80 *V/V*);

— *mobile phase B*: *methanol R2*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	75	25
2 - 2.1	75 → 56	25 → 44
2.1 - 20	56	44

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to fluoxetine (retention time = about 14 min): impurity A = about 0.1; impurity B = about 0.2; impurity C = about 0.9.

System suitability Reference solution (d):

— *peak-to-valley ratio*: minimum 10.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to fluoxetine.

Calculation of percentage contents:

— for impurities A and B, use the concentration of impurity B in reference solution (c);

— for impurities other than A and B, use the concentration of fluoxetine hydrochloride in reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurity A*: maximum 0.15 per cent;

— *impurity B*: maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

Maximum 0.50 per cent, determined on 1.00 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

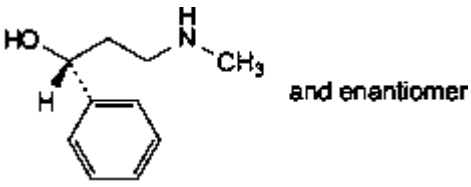
Injection Test solution (b) and reference solution (b).

Calculate the content of $C_{17}H_{19}ClF_3NO$ taking into account the assigned content of *fluoxetine hydrochloride for ID and assay CRS*.

IMPURITIES

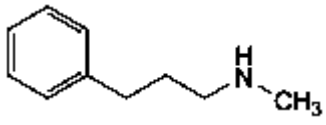
Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C.*



and enantiomer

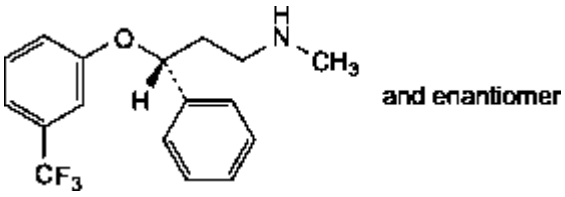
A. (1*RS*)-3-(methylamino)-1-phenylpropan-1-ol,



www.webofpharma.com

https://thuocngocanh.com/

B. *N*-methyl-3-phenylpropan-1-amine,



and enantiomer

C. (3*RS*)-*N*-methyl-3-phenyl-3-[3-(trifluoromethyl)phenoxy]propan-1-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluoxetine Oral Solution

General Notices

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

DEFINITION

Fluoxetine Oral Solution is a solution of Fluoxetine Hydrochloride in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of fluoxetine, $C_{17}H_{18}F_3NO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a volume of the oral solution containing the equivalent of 0.1 g of fluoxetine add 5 mL of 4M *sodium hydroxide*, extract with 10 mL of *dichloromethane*, filter the dichloromethane layer (Whatman 1PS is suitable) and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fluoxetine *(RS 398)*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.5 to 4.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Add 4.33 g of *sodium octanesulfonate* and 13.8 g of *sodium dihydrogen orthophosphate monohydrate* to 1000 mL of *water*, adjust the pH, if necessary, to 3.0 with *orthophosphoric acid* and filter (solution A).

(1) Mix a quantity of the oral solution containing the equivalent of 20 mg of fluoxetine in 20 mL of a mixture of 1 volume of *acetonitrile*, 3 volumes of *methanol* and 6 volumes of solution A and use immediately.

(2) Dilute 1 volume of solution (1) to 25 volumes with a mixture of 1 volume of *acetonitrile*, 3 volumes of *methanol* and 6 volumes of solution A and further dilute 1 volume to 10 volumes with the same solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

(3) Heat a 0.2% w/v solution of *fluoxetine hydrochloride BPCRS* in 0.5M *sulfuric acid* at 85° for 1 hour (generation of impurity A and 4-trifluoromethylphenol).

(4) Dilute 1 volume of solution (3) to 100 volumes with a solution containing 0.1% w/v of *fluoxetine hydrochloride BPCRS* in a mixture of 1 volume of *acetonitrile*, 3 volumes of *methanol* and 6 volumes of solution A.

(5) 0.1% w/v of *fluoxetine hydrochloride BPCRS* and 0.0003% w/v of *fluoxetine impurity C EPCRS* in a mixture of 1 volume of *acetonitrile*, 3 volumes of *methanol* and 6 volumes of solution A.

(6) 0.05% w/v of *benzoic acid* in a mixture of 1 volume of *acetonitrile*, 3 volumes of *methanol* and 6 volumes of solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 20 µL of each solution.

(g) Equilibrate the column with mobile phase A for at least 10 minutes.

MOBILE PHASE

Mobile phase A 21 volumes of *acetonitrile R1*, 26 volumes of *methanol R2* and 53 volumes of solution A.

Mobile phase B 22 volumes of *methanol R2*, 35 volumes of *acetonitrile R1* and 43 volumes of solution A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-13	100	0	isocratic
13-15	100→0	0→100	linear gradient
15-29	0	100	isocratic
29-30	0→100	100→0	linear gradient
30-40	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time of fluoxetine is about 26 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *peak-to-valley ratio* is at least 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to fluoxetine.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any such peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.8%).

Disregard any peak with a retention time corresponding to that of the principal peak in the chromatogram obtained with solution (6).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the oral solution with sufficient of the mobile phase to produce a solution containing the equivalent of 0.004% w/v of fluoxetine.
(2) 0.0045% w/v of *fluoxetine hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed *cyanosilyl silica gel for chromatography* (5 µm) (Dupont Zorbax CN Special is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for at least 10 minutes.

MOBILE PHASE

Equal volumes of a 1% v/v solution of *triethylamine*, adjusted to pH 6.0 with *orthophosphoric acid*, and *acetonitrile R1*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{17}H_{18}F_3NO$, weight in volume, using the declared content of $C_{17}H_{18}F_3NO$,HCl in *fluoxetine hydrochloride BPCRS*. Each mg of $C_{17}H_{18}F_3NO$,HCl is equivalent to 0.8944 mg of $C_{17}H_{18}F_3NO$.

STORAGE

Fluoxetine Oral Solution should be protected from light.

LABELLING

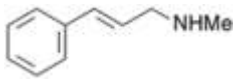
The quantity of active ingredient is stated in terms of the equivalent amount of fluoxetine.

IMPURITIES

www.webofpharma.com

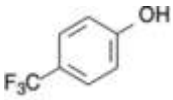
https://thuocngocanh.com/

The impurities limited by the requirements of this monograph include those listed under Fluoxetine Hydrochloride and the following:



1. 3-Methylamino-1-phenylprop-1-ene,

2. 3-Methylamino-1-chloropropane,



3. 4-Trifluoromethylphenol.

© Crown Copyright 2022

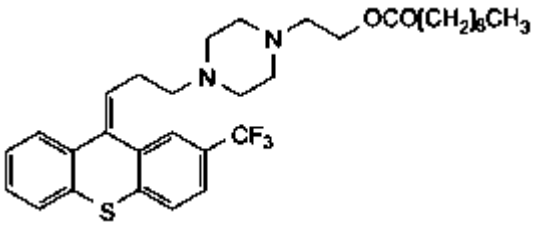
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flupentixol Decanoate

General Notices



$C_{33}H_{43}F_3N_2O_2S$ 588.82 *30909-51-4*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Flupentixol Injection

DEFINITION

Flupentixol Decanoate is (*Z*)-2-{4-[3-(2-trifluoromethylthioxanthen-9-ylidene)propyl]piperazin-1-yl}ethyl decanoate. It contains not less than 98.0% and not more than 101.0% of $C_{33}H_{43}F_3N_2O_2S$, calculated with reference to the dried substance.

CHARACTERISTICS

A yellow, viscous oil.

Very slightly soluble in *water*; soluble in *ethanol (96%)*; freely soluble in *ether*.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 350 nm of a 0.0015% w/v solution in *ethanol (96%)* exhibits two maxima at 230 nm and 264 nm. The *absorbances* at the maxima are about 0.85 and about 0.35, respectively.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of flupentixol decanoate *(RS 154)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *acetonitrile*, protected from light.

www.webofpharma.com

https://thuocngocanh.com/

(1) 0.25% w/v of the substance being examined.

(2) 0.00073% w/v of cis-*flupentixol BPCRS*.

(3) 0.000625% w/v of *2-trifluoromethylthioxanthone BPCRS*.

(4) 0.0025% w/v of trans-*flupentixol decanoate dihydrochloride BPCRS*.

(5) 0.25% w/v of the substance being examined and 0.00073% w/v each of cis-*flupentixol BPCRS, 2-trifluoromethylthioxanthone BPCRS* and 0.0025% w/v of trans-*flupentixol decanoate dihydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable)

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.5 times the retention time of the principal peak.

MOBILE PHASE

0.1 volume of *orthophosphoric acid*, 25 volumes of a 20 millimole solution of *dioctyl sodium sulfosuccinate* (prepared by dissolving 8.89 g of *dioctyl sodium sulfosuccinate* in 500 mL of *water*, stirring for 6 to 8 hours and diluting to 1000 mL with *water*) and *75* volumes of *ethanol (96%)*.

The substances are eluted in the following order: 2-trifluoromethylthioxanthone, *cis*-flupentixol (free alcohol), flupentixol decanoate and *trans*-flupentixol decanoate.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the peaks due to 2-trifluoromethylthioxanthone, *cis*-flupentixol, flupentixol decanoate and *trans*-flupentixol decanoate are clearly separated.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to *cis*-flupentixol is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the area of any peak corresponding to 2-trifluoromethylthioxanthone is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.25%);

the area of any peak corresponding to *trans*-flupentixol decanoate dihydrochloride is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1%);

Loss on drying

When dried at 60° at a pressure of 0.7 kPa for 3 hours, loses not more than 1.0% of its weight. Use 1 g.

www.webofpharma.com

https://thuocngocanh.com/

Sulfated ash

Not more than 0.1%, Appendix IX A.

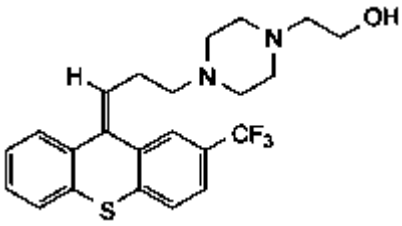
ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.2 g in 50 mL of *anhydrous acetic acid* and determining the end point potentiometrically. Each mL of *0.1M perchloric acid VS* is equivalent to 29.44 mg of $C_{33}H_{43}F_3N_2O_2S$.

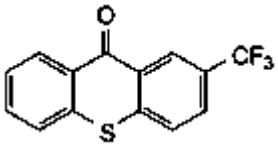
STORAGE

Flupentixol Decanoate should be protected from light and stored at a temperature below -15°.

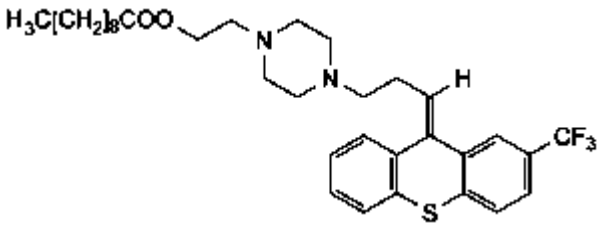
IMPURITIES



A. *cis*-flupentixol (free alcohol),



B. 2-trifluoromethylthioxanthone,



C. *trans*-flupentixol decanoate.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

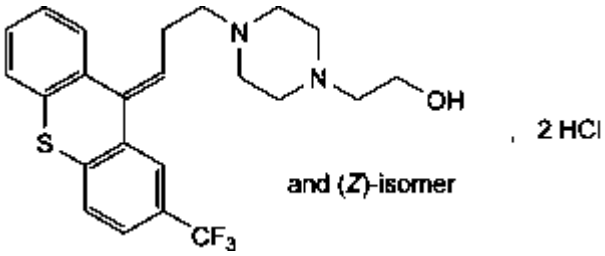
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flupentixol Hydrochloride

General Notices

(Flupentixol Dihydrochloride, Ph. Eur. monograph 1693)



$C_{23}H_{27}Cl_2F_3N_2OS$ 507.4 *2413-38-9*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Flupentixol Tablets

Ph Eur

DEFINITION

2-[4-[3-[(*EZ*)-2-(Trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethan-1-ol dihydrochloride.

Content

— *flupentixol dihydrochloride*: 99.0 per cent to 101.0 per cent (dried substance);

— *(Z)-isomer*: 42.0 per cent to 52.0 per cent.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flupentixol dihydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *flupentixol dihydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *diethylamine R*, *methyl ethyl ketone R* (1:4:95 *V/V/V*).

Application 2 µL.

Development Twice over 3/4 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution. Doubling of the spot may be observed in both chromatograms.

Detection B Spray with *alcoholic solution of sulfuric acid R*; heat at 110 °C for 5 min and allow to cool; examine in ultraviolet light at 365 nm.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution. Doubling of the spot may be observed in both chromatograms.

C. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter and add to the filtrate a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow. The blank is red.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 410 nm is not greater than 0.125.

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.500 g in 5.0 mL of *water R*.

pH (*2.2.3*)

2.0 to 3.0.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light and prepare the solutions immediately before use.*

Buffer solution Dissolve 6.3 g of *ammonium formate R* in about 900 mL of *water for chromatography R*, adjust to pH 8.2 with *concentrated ammonia R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 58.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve the contents of a vial of *flupentixol for system suitability CRS* (containing impurities A, C, H and I) in 1 mL of mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: buffer solution, *acetonitrile for chromatography R*, *water for chromatography R* (58:420:522 *V/V/V*);

— *mobile phase B*: buffer solution, *acetonitrile for chromatography R* (100:900 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	90 → 5	10 → 95

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

www.webofpharma.com

https://thuocngocanh.com/

Identification of peaks Use the chromatogram supplied with *flupentixol for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to both isomers of flupentixol and impurities A, C + I, and H.

Relative retention With reference to flupentixol (*Z*)-isomer (retention time = about 11 min): impurity A = about 0.83; impurity H = about 0.90; impurities C and I = about 0.97; flupentixol (*E*)-isomer = about 1.04.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurities A and H;

— *peak-to-valley ratio*: minimum 10.0, where H_p = height above the baseline of the peak due to impurities C+I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to flupentixol (*Z*)-isomer.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurities C and I = 2.0; impurity H = 2.0;

— for each impurity, use the concentration of flupentixol dihydrochloride (both isomers) in reference solution (a).

Limits:

— *impurity H*: maximum 0.5 per cent;

— *sum of impurities C and I*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 2.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Flupentixol dihydrochloride

Dissolve 0.200 g in 30 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 50.74 mg of $C_{23}H_{27}Cl_2F_3N_2OS$.

www.webofpharma.com

https://thuocngocanh.com/

(*Z*)-Isomer

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution Dissolve 20.0 mg of *flupentixol dihydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm).

Mobile phase *water for chromatography R*, *concentrated ammonia R*, *2-propanol R*, *heptane R* (2:4:150:850 *V/V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 1.5 times the retention time of flupentixol (*Z*)-isomer.

Identification of peaks Use the chromatogram supplied with *flupentixol dihydrochloride CRS* and the chromatogram obtained with the reference solution to identify the peaks due to both isomers of flupentixol.

Relative retention With reference to flupentixol (*Z*)-isomer (retention time = about 6 min): flupentixol (*E*)-isomer = about 1.2.

System suitability Reference solution:

— *resolution*: minimum 3.0 between the peaks due to flupentixol (*Z*)-isomer and flupentixol (*E*)-isomer.

Calculate the percentage content of the (*Z*)-isomer of $C_{23}H_{27}Cl_2F_3N_2OS$ taking into account the assigned content of flupentixol (*Z*)-isomer in *flupentixol dihydrochloride CRS*.

STORAGE

Protected from light.

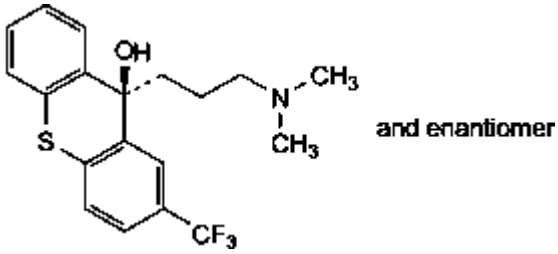
IMPURITIES

Specified impurities *C, H, I.*

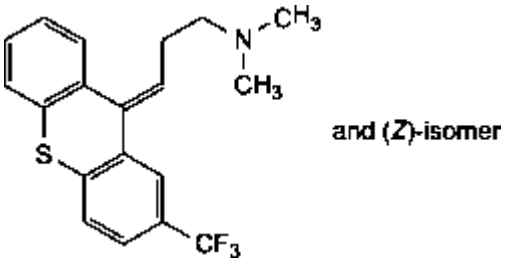
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, E, G.*

www.webofpharma.com

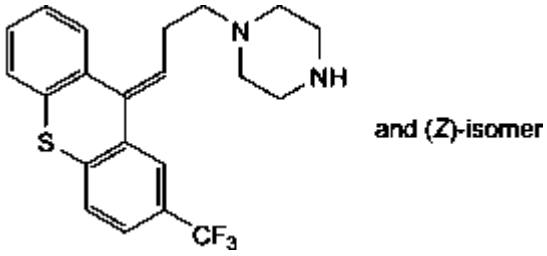
https://thuocngocanh.com/



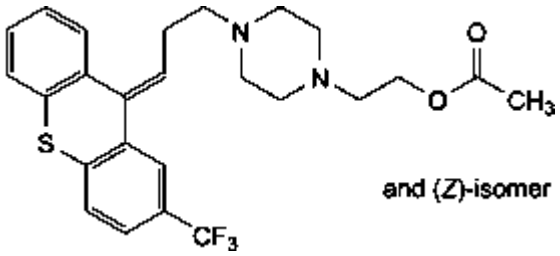
A. (9*RS*)-9-[3-(dimethylamino)propyl]-2-(trifluoromethyl)-9*H*-thioxanthen-9-ol,



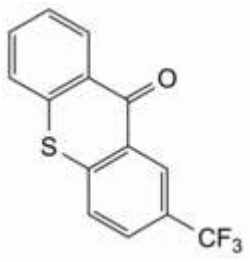
B. *N*,*N*-dimethyl-3-[(*EZ*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propan-1-amine,



C. 1-[3-[(*EZ*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propyl]piperazine,



E. 2-[4-[3-[(*EZ*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethyl acetate,



G. 2-(trifluoromethyl)-9*H*-thioxanthen-9-one,

www.webofpharma.com

https://thuocngocanh.com/

H. either 2-[4-[(*E*)-3-[(9*RS*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-yl]prop-2-en-1-yl]piperazin-1-yl]ethan-1-ol or 2-[4-[(*Z*)-3-[(9*RS*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-yl]prop-2-en-1-yl]piperazin-1-yl]ethan-1-ol,

I. either 2-[4-[(*E*)-3-[(9*RS*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-yl]prop-2-en-1-yl]piperazin-1-yl]ethan-1-ol or 2-[4-[(*Z*)-3-[(9*RS*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-yl]prop-2-en-1-yl]piperazin-1-yl]ethan-1-ol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flupentixol Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Flupentixol Injection is a sterile solution of Flupentixol Decanoate in a suitable vegetable oil.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of flupentixol decanoate, $C_{33}H_{43}F_3N_2O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute 1 volume of solution A obtained in the Assay to 2 volumes with *ethanol (96%)*. The *light absorption*, Appendix II B, in the range 205 to 300 nm of the resulting solution exhibits two maxima at 230 nm and 264 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of 3 volumes of *diethylamine* and 90 volumes of *cyclohexane* as the mobile phase and an unsaturated tank. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) dilute the injection with *ethanol (96%)* to contain 0.4% w/v of flupentixol decanoate. Solution (2) contains 0.4% w/v of *flupentixol decanoate dihydrochloride BPCRS* in *ethanol (96%)*. After removal of the plate, allow it to dry in air, spray with a 1% w/v solution of *sodium molybdate* in *sulfuric acid*, heat at 110° for 20 minutes and examine in daylight. The principal spot in the chromatogram obtained with solution (1) is similar in colour, position and size to that in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *acetonitrile*, protected from light. For solution (1) dilute the injection to contain 0.20% w/v of Flupentixol Decanoate. Solution (2) contains 0.0070% w/v of *cis-flupentixol BPCRS*. Solution (3) contains 0.001% w/v of *2-trifluoromethylthioxanthone BPCRS*. Solution (4) contains 0.002% w/v of *flupentixol decanoate BPCRS*. Solution (5) contains 0.007% w/v of *cis-flupentixol BPCRS* and 0.001% w/v each of *2-trifluoromethylthioxanthone BPCRS* and *flupentixol decanoate BPCRS* in solution (1).

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable) maintained at a temperature of 40°, (b) as the mobile phase with a flow

www.webofpharma.com

https://thuocngocanh.com/

rate of 1 mL per minute a mixture of 0.1 volume of *orthophosphoric acid*, 25 volumes of a 20 millimole solution of *dioctyl sodium sulfosuccinate* (prepared by dissolving 8.89 g of *dioctyl sodium sulfosuccinate* in 500 mL of *water*, stirring for 6 to 8 hours and diluting to 1000 mL with *water*) and 75 volumes of *ethanol (96%)* and (c) a detection wavelength of 270 nm.

Inject solution (1) and allow the chromatography to proceed for 1.5 times the retention time of the principal peak. Inject 20 µL of each solution. The substances are eluted in the following order: 2-trifluoromethylthioxanthone, *cis*-flupentixol (free alcohol), flupentixol decanoate and *trans*-flupentixol decanoate. The test is not valid unless the chromatogram obtained with solution (5) shows clearly separated peaks.

In the chromatogram obtained with solution (1) the area of any peak corresponding to *cis*-flupentixol is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (3%), the area of any peak corresponding to 2-trifluoromethylthioxanthone is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%) and the area of any peak corresponding to *trans*-flupentixol decanoate is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1.0%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *acetonitrile*, protected from light. For solution (1) dilute a volume of the injection to contain 0.20% w/v of Flupentixol Decanoate. Solution (2) contains 0.22% w/v of *flupentixol decanoate dihydrochloride BPCRS*.

The chromatographic procedure described under Related substances may be used.

Calculate the content of $C_{33}H_{43}F_3N_2O_2S$ using the declared content of $C_{33}H_{43}F_3N_2O_2S$ in *flupentixol decanoate dihydrochloride BPCRS*. Each mg of flupentixol decanoate dihydrochloride is equivalent to 0.8897 mg of flupentixol decanoate.

STORAGE

Flupentixol Injection should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flupentixol Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Flupentixol Tablets contain Flupentixol Hydrochloride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of flupentixol, $C_{23}H_{25}F_3N_2OS$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 4 mg of flupentixol with 5 mL of *methanol*, add sufficient *methanol* to produce 10 mL and filter.

(2) 0.05% w/v of *flupentixol dihydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate twice to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *water*, 4 volumes of *diethylamine* and 95 volumes of *methyl ethyl ketone*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2). Doubling of the spots may be observed in each chromatogram.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to flupentixol in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the medium. Carry out the following procedure protected from light and prepare solutions immediately before use.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with sufficient 0.1M *hydrochloric acid*, if necessary, to produce a solution expected to contain the equivalent of 0.0001% w/v of flupentixol.

(2) 0.00012% w/v of *flupentixol dihydrochloride BPCRS*.

(3) 0.058% w/v of *flupentixol dihydrochloride BPCRS* and 0.0005% of *2-trifluoromethylthioxanthone BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 270 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Solution A Dissolve 8.89 g of *dioctyl sodium sulfosuccinate* in 500 mL of *water* (by stirring for approximately 8 hours) and add sufficient *water* to produce 1000 mL.

0.1 volume of *orthophosphoric acid*, 25 volumes of solution A and 75 volumes of *ethanol (96%)*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to flupentixol and 2-trifluoromethylthioxanthone is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of flupentixol (both *E* and *Z* isomers) in the medium using the declared content of $C_{23}H_{25}F_3N_2OS$ in *flupentixol dihydrochloride BPCRS*.

LIMITS

The amount of flupentixol released is not less than 75% (Q) of the stated amount.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing the equivalent of 5 mg of flupentixol with 7 mL of the mobile phase, add sufficient of the mobile phase to produce 10 mL and filter.
(2) Dilute 1 volume of solution (1) to 50 volumes with *mobile phase* and further dilute 1 volume of this solution to 10 volumes with the mobile phase.
(3) 0.0005% w/v of *2-trifluoromethylthioxanthone BPCRS* in the mobile phase.
(4) 0.0058% w/v of *flupentixol dihydrochloride BPCRS* and 0.0005% of *2-trifluoromethylthioxanthone BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used. For solution (1), allow the chromatography to proceed for 3 times the retention time of flupentixol.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to flupentixol *Z*-isomer (retention time, about 10.5 minutes) are: flupentixol *E*-isomer, about 0.85; 2-trifluoromethylthioxanthone, about 0.65.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to flupentixol and 2-trifluoromethylthioxanthone is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-trifluoromethylthioxanthone is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of flupentixol comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse one tablet with 1 mL of *water*, add sufficient *methanol* to produce 10 mL and filter, dilute with sufficient *methanol*, if necessary, to produce a solution expected to contain the equivalent of 0.005% w/v of flupentixol.
(2) 0.0058% w/v of *flupentixol dihydrochloride BPCRS* in *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.0058% w/v each of *flupentixol dihydrochloride BPCRS* and *melitracen hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with end-capped *octadecylsilyl silica gel* (5 µm) (Brownlee Analytical C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

10 volumes of a 0.34% w/v solution of *potassium dihydrogen orthophosphate* and 90 volumes of *methanol*, adjust the pH of the mixture to pH 7.3 with *triethylamine*.

When the chromatograms are recorded under the prescribed conditions, the retention time relative to flupentixol (retention time, about 5 minutes) of melitracen is about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to flupentixol and melitracen is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{25}F_3N_2OS$ (flupentixol) in each tablet using the declared content of $C_{23}H_{25}F_3N_2OS$ in *flupentixol dihydrochloride BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of flupentixol

Use the average of the individual results obtained in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of flupentixol

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *methanol*.

(1) Shake a quantity of powdered tablets containing the equivalent of 5 mg of flupentixol with 25 mL of *methanol*, add sufficient *methanol* to produce 50 mL and filter.

(2) 0.012% w/v of *flupentixol dihydrochloride BPCRS*.

(3) 0.012% w/v each of *flupentixol dihydrochloride BPCRS* and *melitracen hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to flupentixol and melitracen is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{25}F_3N_2OS$ (flupentixol) in the tablets using the declared content of $C_{23}H_{25}F_3N_2OS$ in *flupentixol dihydrochloride BPCRS*.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of flupentixol.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

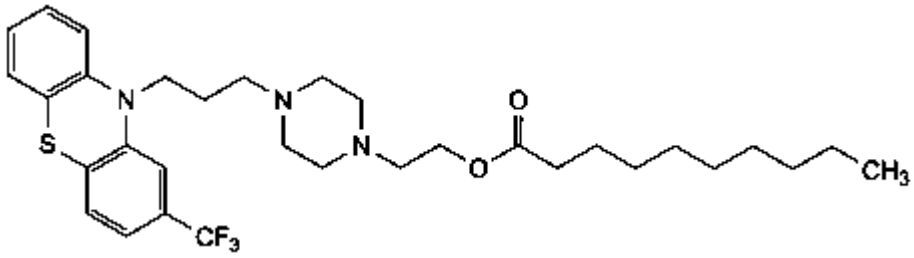
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluphenazine Decanoate

General Notices

(Ph. Eur. monograph 1014)



$C_{32}H_{44}F_3N_3O_2S$ 591.8 *5002-47-1*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Fluphenazine Decanoate Injection

Ph Eur

DEFINITION

2-[4-[3-[2-(Trifluoromethyl)-10*H*-phenothiazin-10-yl]propyl]piperazin-1-yl]ethyl decanoate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow, viscous liquid or yellow solid.

Solubility

Practically insoluble in water, very soluble in anhydrous ethanol and in methylene chloride, freely soluble in methanol.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: B, C.

Second identification: A, C.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *methanol R*.

Spectral range 230-350 nm.

Absorption maximum 260 nm.

Shoulder About 310 nm.

Specific absorbance at the absorption maximum 570 to 630.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Apply 50 µL of a 25 g/L solution in *methylene chloride R* to a disc of *potassium bromide R*. Dry the discs at 60 °C for 1 h before use.

Comparison *fluphenazine decanoate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *fluphenazine decanoate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *fluphenazine enantate CRS* (impurity C) in reference solution (a) and dilute to 5 mL with the same solution.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R1*, *water R*, *methanol R* (1:4:95 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Fluphenazine decanoate = about 0.17; impurity C = about 0.26.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

www.webofpharma.com

https://thuocngocanh.com/

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Solvent mixture A Mobile phase A, mobile phase B (5:95 *V/V*).

Solvent mixture B *water R*, *acetonitrile R* (5:95 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *fluphenazine enantate CRS* (impurity C) and 5 mg of *fluphenazine octanoate CRS* (impurity D) in *acetonitrile R* and dilute to 50 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with solvent mixture A. Dilute 1.0 mL of this solution to 10.0 mL with solvent mixture A.

Reference solution (c) Dissolve 5.0 mg of *fluphenazine sulfoxide CRS* (impurity A) and 11.7 mg of *fluphenazine dihydrochloride CRS* (corresponding to about 10.0 mg of impurity B) in solvent mixture B and dilute to 100.0 mL with solvent mixture B. Dilute 1.0 mL of the solution to 50.0 mL with solvent mixture B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 10 g/L solution of *ammonium carbonate R* adjusted to pH 7.5 with *dilute hydrochloric acid R*;

— *mobile phase B*: mobile phase A, *acetonitrile R*, *methanol R* (7.5:45:45 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	20	80
7 - 17	20 → 0	80 → 100
17 - 80	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 260 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 10 µL.

Relative retention With reference to fluphenazine decanoate (retention time = about 34 min): impurity A = about 0.13; impurity B = about 0.33; impurity C = about 0.76; impurity D = about 0.82.

System suitability Reference solution (a):

— *resolution*: minimum 6.0 between the peaks due to impurities C and D.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

— *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.250 g in 30 mL of *glacial acetic acid R*. Using 0.05 mL of *crystal violet solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from violet to green.

1 mL of *0.1 M perchloric acid* is equivalent to 29.59 mg of $C_{32}H_{44}F_3N_3O_2S$.

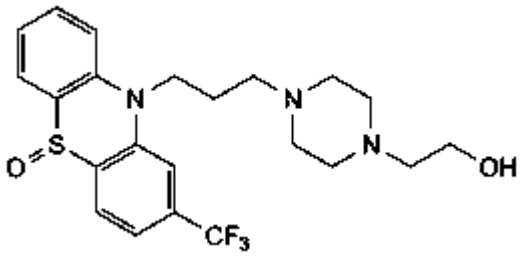
STORAGE

Protected from light.

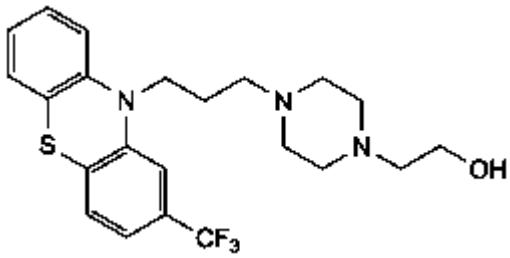
IMPURITIES

www.webofpharma.com

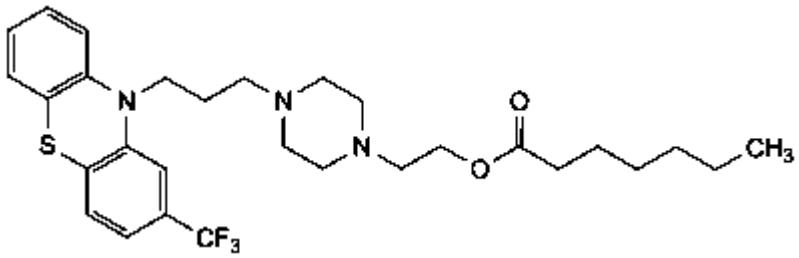
https://thuocngocanh.com/



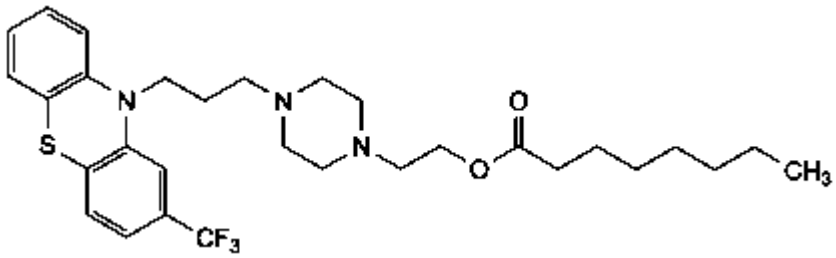
A. fluphenazine *S*-oxide (fluphenazine sulfoxide),



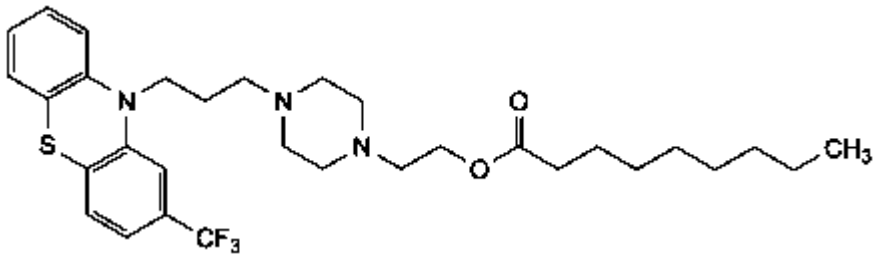
B. fluphenazine,



C. fluphenazine enantate,



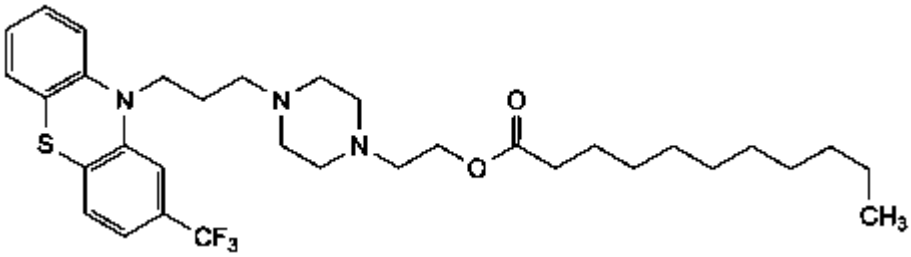
D. fluphenazine octanoate,



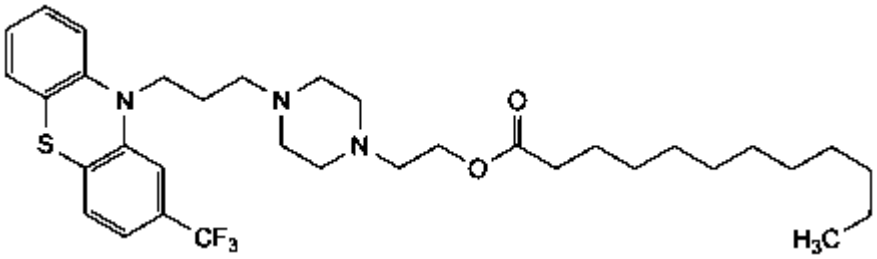
E. fluphenazine nonanoate,

www.webofpharma.com

https://thuocngocanh.com/



F. fluphenazine undecanoate,



G. fluphenazine dodecanoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluphenazine Decanoate Injection

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Fluphenazine Decanoate Injection is a sterile solution of Fluphenazine Decanoate in refined sesame oil.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of fluphenazine decanoate, $C_{32}H_{44}F_3N_3O_2S$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using a plate 200 mm × 200 mm in size and *silica gel* *GF*$_{254}$ as the coating substance. For the first development use *chloroform* as the mobile phase. Apply to the bottom right-hand corner of the plate a volume of the injection containing 25 µg of Fluphenazine Decanoate and develop over a path of 12 cm. After removal of the plate, allow it to dry in air, turn the plate through 90° in a clockwise direction, impregnate the coating with a 5% v/v solution of n-*tetradecane* in n-*hexane* and allow it to dry in air. Apply to the bottom right-hand corner of the plate, to the right of the solvent front of the first development, 1 µL of a 2.0% w/v solution of *fluphenazine decanoate EPCRS* in *ethanol (96%)*. For the second development use *methanol (90%)* as the mobile phase. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with the injection corresponds to that in the chromatogram obtained with the reference substance.

B. Shake a volume containing 5 mg of Fluphenazine Decanoate with 1 mL of a 1% w/v solution of *sucrose* in *hydrochloric acid* and allow to stand for 5 minutes. A red colour is produced in the acid layer.

Related substances

Protect the solutions from light. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute a volume of the injection with sufficient *chloroform* to produce a solution containing 0.50% w/v of Fluphenazine Decanoate, dilute 1 volume of this solution to 25 volumes with *acetonitrile* and mix. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*. For solution (3) add 0.05 mL of 10M *sodium hydroxide* to 2 mL of solution (1) and allow to stand for 48 hours before use (generation of fluphenazine impurity). For solution (4) add 0.05 mL of *hydrogen peroxide solution (200 vol)* to 5 mg of *fluphenazine decanoate EPCRS*, allow to stand for 10 minutes, add sufficient *chloroform* to produce 1 mL, mix and dilute to 100 mL with *acetonitrile* (generation of mono- and di-*N*-oxide impurities).

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable) fitted with a guard column (2.5 cm × 4.6 mm) packed with the same material, (b) as the mobile phase with a flow rate of 1 mL per minute a solution prepared by adding 450 volumes of *acetonitrile* to a mixture of 75 volumes of a 1% w/v solution of *ammonium carbonate* and 450 volumes of *methanol* adjusted to pH 7.5 with 1M *acetic acid* and (c) a detection wavelength of 260 nm.

Inject separately 20 µL of each solution. After completion of the test, flush the column with a mixture of equal volumes of *methanol* and *water*.

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to the two fluphenazine mono-*N*-oxides is at least 2.

In the chromatogram obtained with solution (1) the area of any peak corresponding to the peak due to fluphenazine impurity in the chromatogram obtained with solution (3) is not greater than 4 times the area of the peak in the chromatogram obtained with solution (2) (4%), the area of any other *secondary peak* is not greater than the area of the peak in the chromatogram obtained with solution (2) (1%) and the sum of the areas of any *secondary peaks* other than any peak corresponding to fluphenazine is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (2%). Disregard any peak with a retention time relative to fluphenazine decanoate of 0.2 or less.

ASSAY

Carry out Method I for *non-aqueous titration*, Appendix VIII A, using a volume containing 0.15 g of Fluphenazine Decanoate diluted with 75 mL of *anhydrous acetic acid* and *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 29.59 mg of $C_{32}H_{44}F_3N_3O_2S$.

STORAGE

Fluphenazine Decanoate Injection should be protected from light.

LABELLING

The label states that the injection is for intramuscular injection only.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

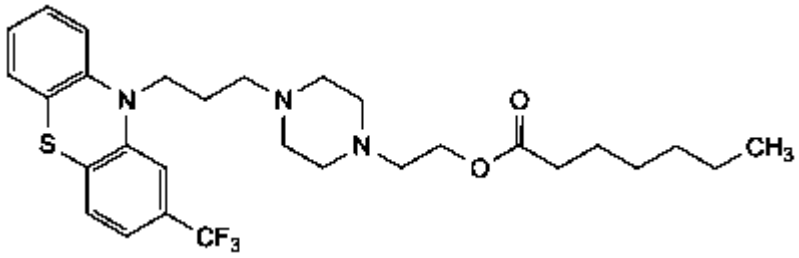
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluphenazine Enantate

General Notices

(Ph. Eur. monograph 1015)



$C_{29}H_{38}F_3N_3O_2S$ 549.7 *2746-81-8*

Action and use

Dopamine receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

2-[4-[3-[2-(Trifluoromethyl)-10*H*-phenothiazin-10-yl]propyl]piperazin-1-yl]ethyl heptanoate.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow, viscous liquid or yellow solid.

Solubility

Practically insoluble in water, very soluble in anhydrous ethanol and in methylene chloride, freely soluble in methanol.

IDENTIFICATION

First identification: B, C.

Second identification: A, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *methanol R*.

Spectral range 230-350 nm.

Absorption maximum 260 nm.

Shoulder About 310 nm.

Specific absorbance at the absorption maximum 610 to 670.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Apply 50 µL of a 25 g/L solution in *methylene chloride R* to a disc of *potassium bromide R*. Dry the discs at 60 °C for 1 h before use.

Comparison *fluphenazine enantate CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *fluphenazine enantate CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *fluphenazine decanoate CRS* (impurity C) in reference solution (a) and dilute to 5 mL with the same solution.

Plate *TLC octadecylsilyl silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R1*, *water R*, *methanol R* (1:4:95 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Impurity C = about 0.17; fluphenazine enantate = about 0.26.

Sytem suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Solvent mixture Mobile phase A, mobile phase B (5:95 *V/V*).

Test solution Dissolve 10.0 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *fluphenazine enantate CRS* and 5 mg of *fluphenazine octanoate CRS* (impurity D) in *acetonitrile R* and dilute to 50 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5.0 mg of *fluphenazine sulfoxide CRS* (impurity A) in *acetonitrile R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 50.0 mL with *acetonitrile R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: 10 g/L solution of *ammonium carbonate R* adjusted to pH 7.5 with *dilute hydrochloric acid R*;

— *mobile phase B*: mobile phase A, *acetonitrile R*, *methanol R* (7.5:45:45 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	20	80
7 - 17	20 → 0	80 → 100
17 - 80	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 10 µL.

Relative retention With reference to fluphenazine enantate (retention time = about 25 min): impurity A = about 0.2; impurity D = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 6.0 between the peaks due to fluphenazine enantate and impurity D.

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *total*: not more than 3.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.6 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

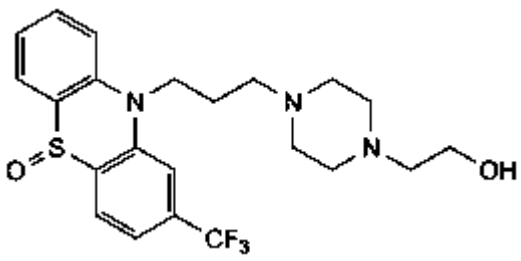
Dissolve 0.250 g in 30 mL of *glacial acetic acid R*. Using 0.05 mL of *crystal violet solution R* as indicator, titrate with *0.1 M perchloric acid* until the colour changes from violet to green.

1 mL of *0.1 M perchloric acid* is equivalent to 27.49 mg of $C_{29}H_{38}F_3N_3O_2S$.

STORAGE

Protected from light.

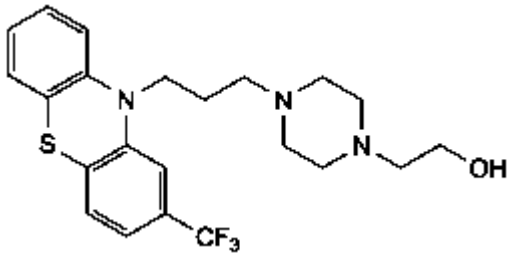
IMPURITIES



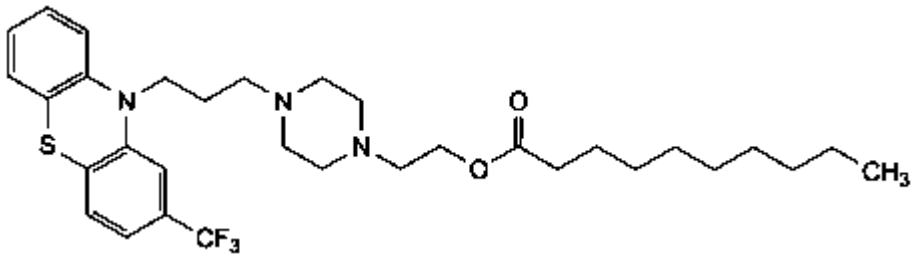
A. fluphenazine *S*-oxide (fluphenazine sulfoxide),

www.webofpharma.com

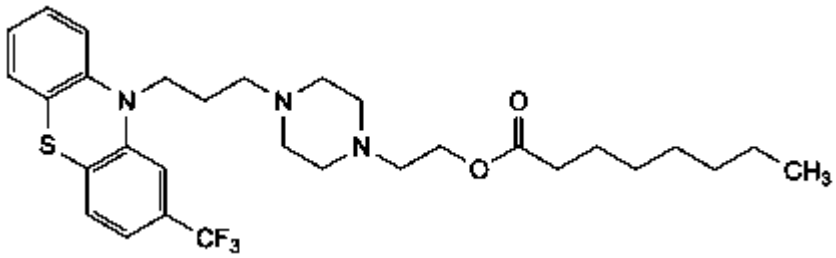
https://thuocngocanh.com/



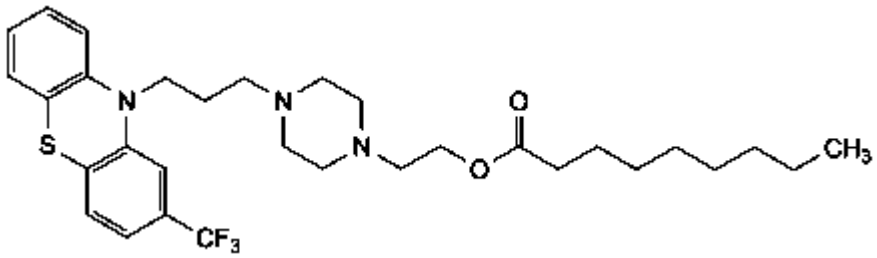
B. fluphenazine,



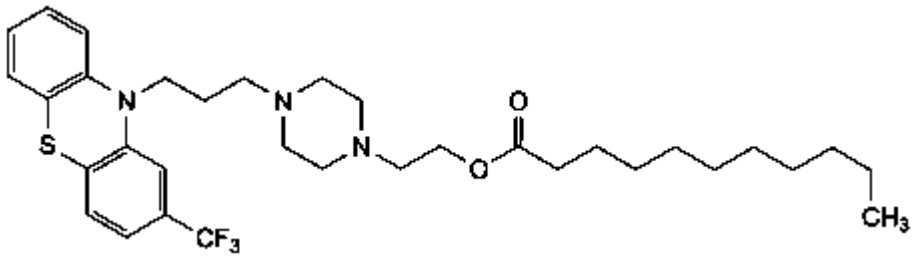
C. fluphenazine decanoate,



D. fluphenazine octanoate,



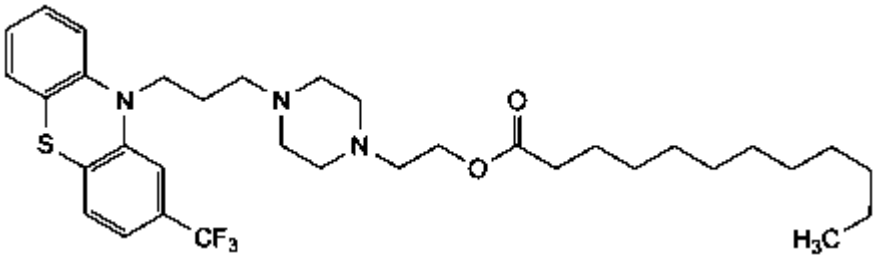
E. fluphenazine nonanoate,



F. fluphenazine undecanoate,

www.webofpharma.com

https://thuocngocanh.com/



G. fluphenazine dodecanoate.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

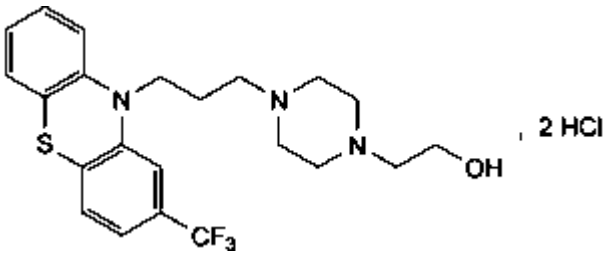
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluphenazine Hydrochloride

General Notices

(Fluphenazine Dihydrochloride, Ph. Eur. monograph 0904)



$C_{22}H_{28}Cl_2F_3N_3OS$ 510.4 *146-56-5*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Fluphenazine Tablets

Ph Eur

DEFINITION

2-[4-[3-[2-(Trifluoromethyl)-10*H*-phenothiazin-10-yl]propyl]piperazin-1-yl]ethanol dihydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in methanol R and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with methanol R.

Spectral range 230-350 nm.

Absorption maxima At 260 nm and at about 310 nm (broad band).

Specific absorbance at the absorption maximum at 260 nm 630 to 700.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison fluphenazine dihydrochloride CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of fluphenazine dihydrochloride CRS in methanol R and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of perphenazine CRS in reference solution (a) and dilute to 5 mL with reference solution (a).

Plate TLC octadecylsilyl silica gel F_{254} plate R.

Mobile phase concentrated ammonia R1, water R, methanol R (1:4:95 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

www.webofpharma.com

https://thuocngocanh.com/

1.9 to 2.4.

Dissolve 0.5 g in 10 mL of *water R*.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light and prepare the solutions immediately before use.*

Solution A Mix 4 mL of *acetic acid R* and 996 mL of a 4.33 g/L solution of *sodium octanesulfonate R*.

Test solution Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 5.0 mL of this solution to 25.0 mL with mobile phase A.

Reference solution (b) Dissolve the contents of a vial of *fluphenazine impurity mixture CRS* (impurities A, B, C and D) in 5 mL of the test solution and sonicate for 1 min. Mix 1.0 mL of this solution and 1.0 mL of the test solution.

Reference solution (c) Dissolve 5.0 mg of *fluphenazine sulfoxide CRS* (impurity A) in mobile phase A and dilute to 50.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetic acid R*, *methanol R*, *acetonitrile R*, solution A (0.2:15:40:45 *V/V/V/V*);

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 35	100 → 30	0 → 70
35 - 50	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 260 nm and at 274 nm.

Injection 10 µL.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *fluphenazine impurity mixture CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to fluphenazine (retention time = about 19 min): impurity A = about 0.2; impurity B = about 0.3; impurity D = about 2.0; impurity C = about 2.1.

System suitability Reference solution (b):

— *resolution at 274 nm*: minimum 2.5 between the peaks due to impurities A and B.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.3; impurity C = 0.6;

— *impurity A at 274 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity B at 274 nm*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities C, D at 260 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities at 260 nm*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of the impurities other than A and B at 260 nm and impurities A and B at 274 nm*: not more than 1.0 per cent;

— *disregard limit at 260 nm*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 65 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

In order to avoid overheating during the titration, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.220 g in a mixture of 10 mL of *anhydrous formic acid R* and 40 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

www.webofpharma.com

https://thuocngocanh.com/

1 mL of *0.1 M perchloric acid* is equivalent to 25.52 mg of $C_{22}H_{28}Cl_2F_3N_3OS$.

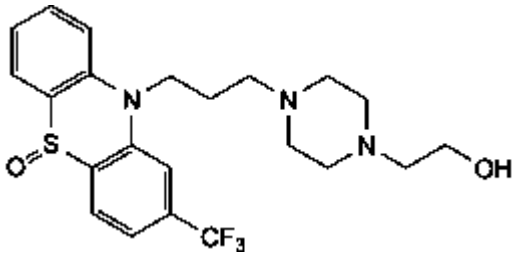
STORAGE

Protected from light.

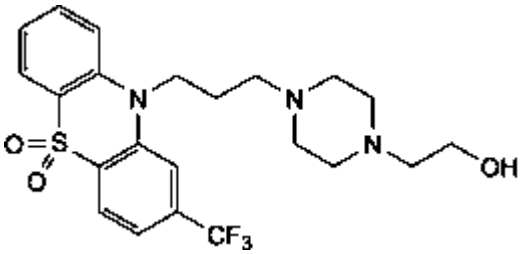
IMPURITIES

Specified impurities *A, B, C, D.*

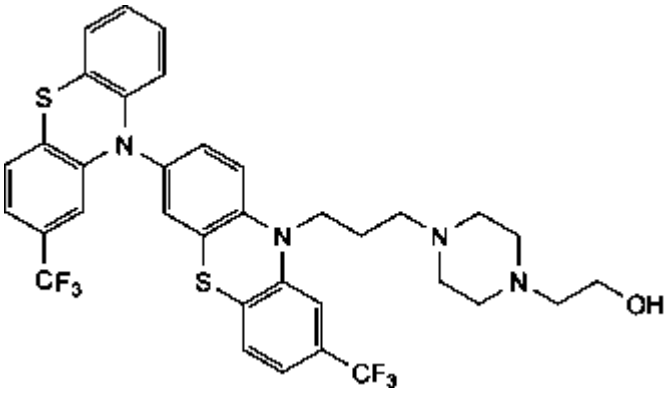
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *E, F.*



A. 2-[4-[3-[5-oxo-2-(trifluoromethyl)-10*H*-5λ^4-phenothiazin-10-yl]propyl]piperazin-1-yl]ethanol (fluphenazine *S*-oxide),



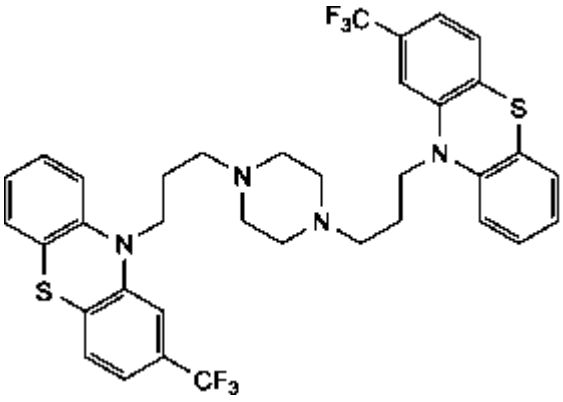
B. 2-[4-[3-[5,5-dioxo-2-(trifluoromethyl)-10*H*-5λ^6-phenothiazin-10-yl]propyl]piperazin-1-yl]ethanol (fluphenazine *S,S*-dioxide),



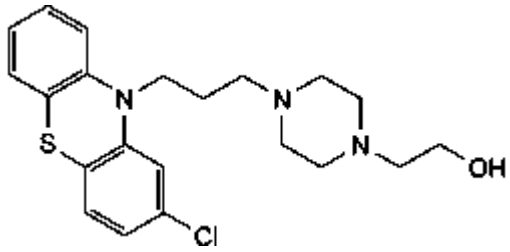
C. 2-[4-[3-[2′,8-bis(trifluoromethyl)-10*H*-3,10′-biphenothiazin-10-yl]propyl]piperazin-1-yl]ethanol,

www.webofpharma.com

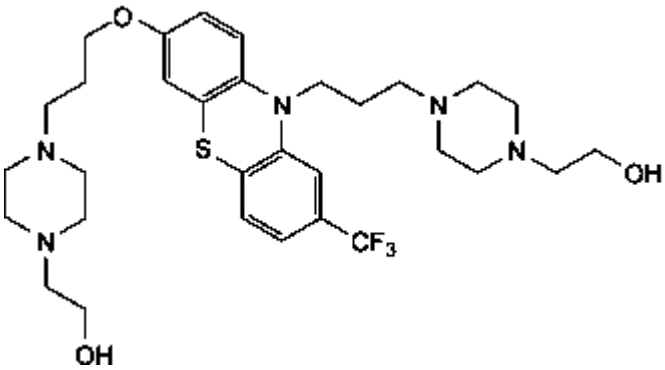
https://thuocngocanh.com/



D. 10,10′-[piperazine-1,4-diylbis(propane-3,1-diyl)]bis[2-(trifluoromethyl)-10*H*-phenothiazine],



E. 2-[4-[3-[2-chloro-10*H*-phenothiazin-10-yl]propyl]piperazin-1-yl]ethanol (perphenazine),



F. 2-[4-[3-[7-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy]-2-(trifluoromethyl)-10*H*-phenothiazin-10-yl]propyl]piperazin-1-yl)ethanol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluphenazine Tablets

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Fluphenazine Tablets contain Fluphenazine Hydrochloride. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of fluphenazine hydrochloride, $C_{22}H_{26}F_3N_3OS,2HCl$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Shake a quantity of the powdered tablets with sufficient *methanol* to produce a solution containing 0.2% w/v of Fluphenazine Hydrochloride, centrifuge and use the supernatant liquid.

(2) 0.2% w/v of *fluphenazine hydrochloride BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *kieselguhr G*. Impregnate the dry plate by placing it in a tank containing a shallow layer of a mixture of 5 volumes of *2-phenoxyethanol*, 15 volumes of *formamide* and 180 volumes of *acetone*, allowing the impregnating solvent to ascend to the top, removing the plate from the tank and using it immediately.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, examine under *ultraviolet light (365 nm)* and observe the fluorescence produced after about 2 minutes. Heat the plate at 120° for 20 minutes, cool, spray with *ethanolic sulfuric acid (20%)* and observe the colour produced.

MOBILE PHASE

2 volumes of *diethylamine* and 100 volumes of *petroleum spirit (boiling range, 40° to 60°)* saturated with *2-phenoxyethanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, fluorescence and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. Extract a quantity of the powdered tablets containing 5 mg of Fluphenazine Hydrochloride with 5 mL of *acetone*, filter and evaporate the filtrate to dryness. Add 2 mL of *sulfuric acid* to the residue and allow to stand for 5 minutes. An orange colour is produced.

C. Extract a quantity of the powdered tablets containing 10 mg of Fluphenazine Hydrochloride with 10 mL of *absolute ethanol* containing 0.2% v/v of 13.5M *ammonia* and evaporate the extract to dryness. Heat 0.5 mL of *chromic–sulfuric acid mixture* in a small test tube in a water bath for 5 minutes; the solution wets the side of the tube readily and there is no greasiness. Add 2 or 3 mg of the residue and again heat in a water bath for 5 minutes; the solution does not wet the side of the tube and does not pour easily from the tube.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Remove the coating from a suitable number of tablets; shake a quantity of the powdered tablet cores containing 20 mg of Fluphenazine Hydrochloride with 10 mL of 0.1M *methanolic sodium hydroxide* for 5 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 50 volumes with 0.1M *methanolic sodium hydroxide*.

(3) Dilute 1 volume of solution (1) to 100 volumes with 0.1M *methanolic sodium hydroxide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 50 µL of solution (1). Apply 25 µL of solutions (2) and (3).

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of 13.5M *ammonia*, 30 volumes of *cyclohexane* and 80 volumes of *acetone*.

LIMITS

Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1%) and not more than two such spots are more intense than the spot in the chromatogram obtained with solution (3) (0.5%). Disregard any spot remaining on the line of application.

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Fluphenazine Hydrochloride comply with the requirements stated under Tablets using the following method of analysis. Carry out the following procedure protected from light. Record *second-derivative ultraviolet absorption spectra* of the following solutions in the range 230 to 300 nm, Appendix II B. For solution (1) add 2 mL of 0.1M *hydrochloric acid* to one tablet and mix with the aid of ultrasound until the tablet is dispersed. Add 60 mL of a mixture of 1 volume of 1M *hydrochloric acid* and 99 volumes of *ethanol (80%)*, shake for 20 minutes, dilute to 100 mL with the same solvent mixture, mix and filter. Solution (2) contains 0.001% w/v of *fluphenazine hydrochloride BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

For each solution measure the amplitude from the peak at about 266 nm to the trough at about 258 nm. Calculate the content of $C_{22}H_{26}F_3N_3OS,2HCl$ in each tablet using the declared content of $C_{22}H_{26}F_3N_3OS,2HCl$ in *fluphenazine hydrochloride BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Fluphenazine Hydrochloride

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Fluphenazine Hydrochloride

Carry out the following procedure protected from light. Record *second-derivative ultraviolet absorption spectra* of the following solutions in the range 230 to 300 nm, Appendix II B. For solution (1) add 20 mL of 0.1M *hydrochloric acid* to 10 tablets, mix with the aid of ultrasound until the tablets are dispersed, add 600 mL of a mixture of 1 volume of 1M *hydrochloric acid* and 99 volumes of *ethanol (80%)*, shake for 20 minutes, dilute to 1000 mL with the same solvent mixture, mix and filter. Solution (2) contains 0.001% w/v of *fluphenazine hydrochloride BPCRS*.

For each solution measure the amplitude from the peak at about 266 nm to the trough at about 258 nm. Calculate the content of $C_{22}H_{26}F_3N_3OS,2HCl$ in the tablets using the declared content of $C_{22}H_{26}F_3N_3OS,2HCl$ in *fluphenazine hydrochloride BPCRS*.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flurazepam Capsules

General Notices

Action and use

Benzodiazepine.

DEFINITION

Flurazepam Capsules contain Flurazepam Monohydrochloride.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of flurazepam, $C_{21}H_{23}ClFN_3O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the contents of the capsules containing the equivalent of 0.15 g of flurazepam with 3 mL of *chloroform IR* and filter. The *infrared absorption spectrum* of the filtrate, Appendix II A, is concordant with the *reference spectrum* of flurazepam monohydrochloride *(RS 155)*.

B. The *light absorption*, Appendix II B, in the range 220 to 350 nm of the final solution obtained in the Assay exhibits two maxima, at 240 nm and 284 nm.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 2.5 volumes of *diethylamine* and 97.5 volumes of *ether* as the mobile phase. Apply separately to the plate 10 µL of each of the following solutions. For solution (1) shake vigorously a quantity of the contents of the capsules containing the equivalent of 0.1 g of flurazepam with 2 mL of a mixture of 2 volumes of 13.5M *ammonia* and 98 volumes of *methanol* and centrifuge. For solution (2) dilute 1 volume of solution (1) to 200 volumes with the same solvent mixture. After removal of the plate, dry it in a current of air and examine under *ultraviolet light (254 nm)*. Any *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the following procedure protected from light. Transfer a quantity of the capsule contents containing the equivalent of 0.1 g of flurazepam into about 150 mL of 1M *methanolic sulfuric acid*, washing the inner surfaces of the capsule shells, shake for 10 minutes and

www.webofpharma.com

https://thuocngocanh.com/

add sufficient 1M *methanolic sulfuric acid* to produce 250 mL. Further dilute this solution with 1M *methanolic sulfuric acid* to produce a solution containing the equivalent of about 0.002% w/v of flurazepam and measure the *absorbance* of the resulting solution at the maximum at 284 nm, Appendix II B. Calculate the content of $C_{21}H_{23}ClFN_3O$ taking 319 as the value of A(1%, 1 cm) at the maximum at 284 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of flurazepam.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

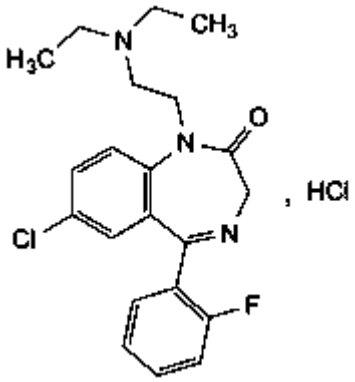
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Flurazepam Monohydrochloride

General Notices

(Ph. Eur. monograph 0905)



$C_{21}H_{24}Cl_2FN_3O$ 424.3 *36105-20-1*

Action and use

Benzodiazepine.

Preparation

Flurazepam Capsules

Ph Eur

DEFINITION

7-Chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one monohydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of flurazepam monohydrochloride*.

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (2.2.3)

5.0 to 6.0.

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of *oxazepam R* in 10 mL of *acetonitrile R* and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 350 volumes of *acetonitrile R* and 650 volumes of a 10.5 g/L solution of *potassium dihydrogen phosphate R* and ajust to pH 6.1 with a 40 g/L solution of *sodium hydroxide R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 239 nm.

Injection 20 µL.

Run time: 6 times the retention time of flurazepam.

Relative retention With reference to flurazepam (retention time = about 7 min): impurity C = about 1.5; impurity B = about 1.9; impurity A = about 2.4.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (b):

— *resolution*: minimum of 4.5 between the peaks due to flurazepam and to oxazepam.

Limits:

— *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 0.61; impurity C = 0.65,

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Fluorides (2.4.5)

Maximum 500 ppm.

0.10 g complies with the limit test for fluorides.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.350 g in a mixture of 1.0 mL of *0.1 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (2.2.20), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 42.43 mg of $C_{21}H_{24}Cl_2FN_3O$.

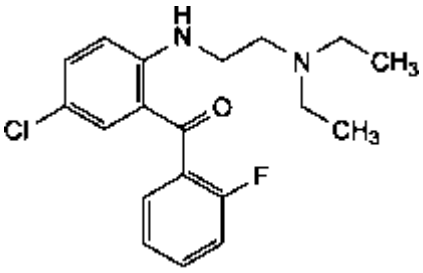
STORAGE

Protected from light.

IMPURITIES

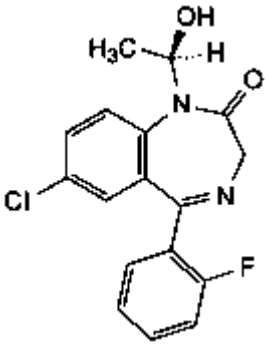
www.webofpharma.com

https://thuocngocanh.com/



A. [5-chloro-2-[[2-(diethylamino)ethyl]amino]phenyl](2-fluorophenyl)methanone,

B. 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,



C. 7-chloro-5-(2-fluorophenyl)-1-[(1*RS*)-1-hydroxyethyl]-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

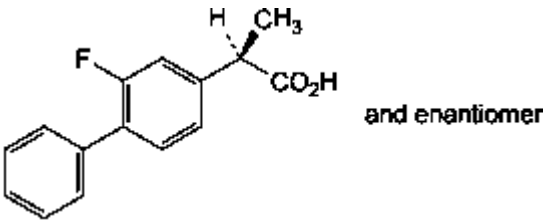
https://thuvienthuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flurbiprofen

General Notices

(Ph. Eur. monograph 1519)



$C_{15}H_{13}FO_2$ 244.3 *5104-49-4*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparation

Flurbiprofen Tablets

Ph Eur

DEFINITION

(2*RS*)-2-(2-Fluoro[1,1′-biphenyl]-4-yl)propanoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flurbiprofen CRS*.

B. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter. To a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*, add 1.0 mL of the filtrate. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method I).

Dissolve 1.0 g in *methanol R* and dilute to 10 mL with the same solvent.

Optical rotation (2.2.7)

-0.1° to + 0.1°.

Dissolve 0.50 g in *methanol R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture *acetonitrile R*, *water R* (45:55 *V/V*).

Test solution Dissolve 0.20 g of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 10.0 mg of *flurbiprofen impurity A CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 10.0 mL of the solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 10 mL with reference solution (b).

Reference solution (d) Dissolve 10 mg of *flurbiprofen for peak identification CRS* (containing impurity B) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *glacial acetic acid R*, *acetonitrile R*, *water for chromatography R* (5:35:60 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time Twice the retention time of flurbiprofen.

Identification of impurities Use the chromatogram supplied with *flurbiprofen for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to flurbiprofen (retention time = about 25 min): impurity B = about 0.8; impurity A = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity A and flurbiprofen.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (b);

— for impurities other than A, use the concentration of flurbiprofen in reference solution (a).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity B*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.7 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying at 60 °C at a pressure not exceeding 0.7 kPa for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

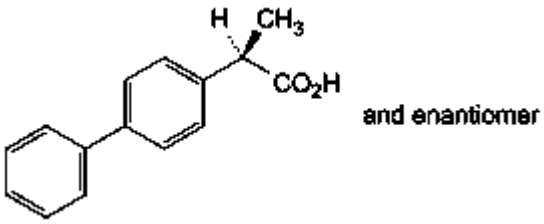
Dissolve 0.200 g in 50 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 24.43 mg of $C_{15}H_{13}FO_2$.

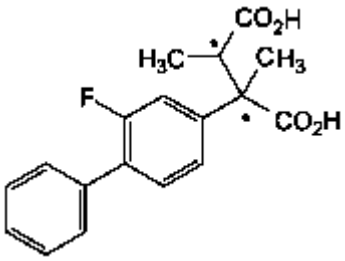
IMPURITIES

Specified impurities *A, B.*

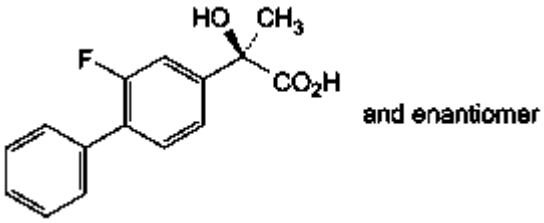
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, D, E.*



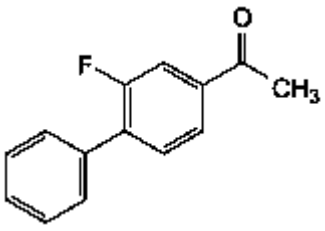
A. (2*RS*)-2-([1,1′-biphenyl]-4-yl)propanoic acid,



B. (2*Ξ*,3*Ξ*)-2-(2-fluoro[1,1′-biphenyl]-4-yl)-2,3-dimethylbutanedioic acid,



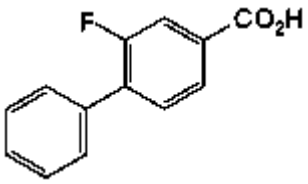
C. (2*RS*)-2-(2-fluoro[1,1′-biphenyl]-4-yl)-2-hydroxypropanoic acid,



www.webofpharma.com

https://thuocngocanh.com/

D. 1-(2-fluoro[1,1′-biphenyl]-4-yl)ethan-1-one,



E. 2-fluoro[1,1′-biphenyl]-4-carboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flurbiprofen Eye Drops

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Flurbiprofen Eye Drops are a sterile solution of Flurbiprofen Sodium in purified water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of flurbiprofen sodium dihydrate, $C_{15}H_{12}FNaO_2,2H_2O$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 5 volumes of *propan-2-ol* and 95 volumes of *dichloromethane* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) dilute the eye drops, if necessary, with a mixture of 25 volumes of *water* and 50 volumes of *methanol* to produce a solution containing 0.01% w/v of flurbiprofen sodium. Solution (2) contains 0.01% w/v of *flurbiprofen sodium BPCRS* in a mixture of 25 volumes of *water* and 50 volumes of *methanol*. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 7.0, Appendix V L.

2-(Biphenyl-4-yl)propionic acid

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute the eye drops, if necessary, with a mixture of 25 volumes of *water* and 50 volumes of *methanol* to produce a solution containing 0.030% w/v of flurbiprofen sodium. Solution (2) contains 0.00015% w/v of *2-(biphenyl-4-yl)propionic acid BPCRS* in a mixture of 25 volumes of *water* and 50 volumes of *methanol*. Solution (3) contains 0.00050% w/v of *flurbiprofen sodium BPCRS* and 0.00050% w/v of *2-(biphenyl-4-yl)propionic acid BPCRS* in a mixture of 25 volumes of *water* and 50 volumes of *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Resolve 5µ is suitable), (b) a mixture of 5 volumes of *glacial acetic acid*, 35 volumes of *acetonitrile* and 60 volumes of *water* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm. Adjust the sensitivity so that the heights of the principal peaks in the chromatogram obtained with solution (3) are about 40% of full-scale deflection on the chart paper.

The test is not valid unless the *resolution factor* between the two principal peaks in the chromatogram obtained with solution (3) is at least 1.5.

In the chromatogram obtained with solution (1) the area of any peak corresponding to 2-(biphenyl-4-yl)propionic acid is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) dilute the eye drops, if necessary, with a mixture of 25 volumes of *water* and 50 volumes of *methanol* to produce a solution containing 0.015% w/v of flurbiprofen sodium. Solution (2) contains 0.015% w/v of *flurbiprofen sodium BPCRS* in a mixture of 25 volumes of *water* and 50 volumes of *methanol*. Solution (3) contains 0.0005% w/v of *flurbiprofen sodium BPCRS* and 0.0005% w/v of *2-(biphenyl-4-yl)propionic acid BPCRS* in a mixture of 25 volumes of *water* and 50 volumes of *methanol*.

The chromatographic procedure described under the test for 2-(Biphenyl-4-yl)propionic acid may be used.

The assay is not valid unless the *resolution factor* between the two principal peaks in the chromatogram obtained with solution (3) is at least 1.5.

Calculate the content of $C_{15}H_{12}FNaO_2,2H_2O$ in the eye drops using the declared content of $C_{15}H_{12}FNaO_2,2H_2O$ in *flurbiprofen sodium BPCRS*.

© Crown Copyright 2022

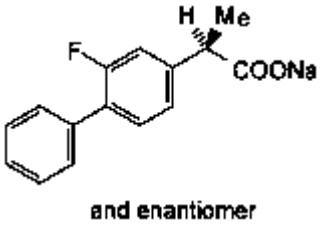
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flurbiprofen Sodium

General Notices



and enantiomer

$C_{15}H_{12}FNaO_2,2H_2O$ 302.3 *56767-76-1*

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Preparation

Flurbiprofen Eye Drops

DEFINITION

Flurbiprofen Sodium is sodium (*RS*)-2-(2-fluorobiphenyl-4-yl)propionate dihydrate. It contains not less than 98.5% and not more than 101.5% of $C_{15}H_{12}FNaO_2$, calculated with reference to the dried substance.

CHARACTERISTICS

A white to creamy-white, crystalline powder.

Sparingly soluble in *water*; soluble in *ethanol (96%)*; practically insoluble in *dichloromethane*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of flurbiprofen sodium (*RS 157*).

B. Heat 0.2 g over a flame until charred and then heat at 600° for 2 hours. The residue yields the reactions characteristic of *sodium salts*, Appendix VI.

TESTS

Related substances

www.webofpharma.com

https://thietbiuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 25 volumes of *water* and 50 volumes of *methanol*.

(1) 0.10% w/v of the substance being examined.

(2) 0.00020% w/v of the substance being examined.

(3) 0.00050% w/v of *2-(biphenyl-4-yl)propionic acid BPCRS*.

(4) 0.00050% w/v of the substance being examined and 0.00050% w/v of *2-(biphenyl-4-yl)propionic acid BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Resolve 5µ is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *glacial acetic acid*, 35 volumes of *acetonitrile* and 60 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the two principal peaks is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-(biphenyl-4-yl)propionic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than five times the area of the peak in the chromatogram obtained with solution (2) (1%).

Loss on drying

11.3% to 12.5% when determined by drying over *phosphorus pentoxide* at 60° at a pressure of 2 kPa for 18 hours. Use 1 g.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 25 volumes of *water* and 50 volumes of *methanol*.

www.webofpharma.com

https://thuocngocanh.com/

(1) 0.015% w/v of the substance being examined.

(2) 0.015% w/v of *flurbiprofen sodium BPCRS*.

(3) 0.00075% w/v of the substance being examined and 0.00075% w/v of *2-(biphenyl-4-yl)propionic acid BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

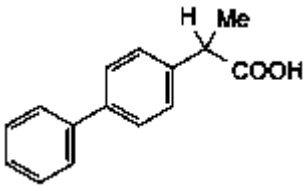
SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{12}FNaO_2$ in the substance being examined using the declared content of $C_{15}H_{12}FNaO_2$ in *flurbiprofen sodium BPCRS*.

IMPURITIES



A. 2-(biphenyl-4-yl)propionic acid.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flurbiprofen Tablets

General Notices

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Flurbiprofen Tablets contain Flurbiprofen. They are coated.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of flurbiprofen, $C_{15}H_{13}FO_2$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.5 g of flurbiprofen with 25 mL of *acetone*, filter, evaporate the filtrate to dryness with the aid of a current of air without heating and dry at 60° at a pressure of 2 kPa. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of flurbiprofen *(RS 156)*.

B. Heat 0.5 mL of *chromic–sulfuric acid mixture* in a small test tube in a water bath for 5 minutes; the solution wets the side of the tube readily and there is no greasiness. Add 2 or 3 mg of the residue and heat in a water bath for 5 minutes; the solution does not wet the side of the tube and does not pour easily from the tube.

C. *Melting point*, about 114°, Appendix V A.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) disperse a quantity of the powdered tablets containing 0.5 g of flurbiprofen in 50 mL of *water*, add 200 mL of *acetonitrile*, mix, centrifuge and use the supernatant liquid. For solution (2) dilute 1 volume of solution (1) to 100 volumes with a mixture of 45 volumes of *acetonitrile* and 55 volumes of *water* and further dilute 1 volume to 5 volumes with the same solvent mixture. Solution (3) contains 0.0010% w/v of *2-(biphenyl-4-yl)propionic acid BPCRS* in a mixture of 45 volumes of *acetonitrile* and 55 volumes of *water*. For solution (4) dilute 1 volume of solution (1) to 200 volumes with solution (3).

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Resolve 5µ is suitable), (b) a mixture of 5 volumes of *glacial acetic acid*, 35 volumes of *acetonitrile* and 60 volumes of *water* as the mobile phase with a flow rate of 1 mL per minute and (c) a detection wavelength of 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Adjust the sensitivity so that the heights of the principal peaks in the chromatogram obtained with solution (4) are about 40% of full-scale deflection on the chart paper.

The test is not valid unless the *resolution factor* between the two principal peaks in the chromatogram obtained with solution (4) is at least 1.5.

In the chromatogram obtained with solution (1) the area of any peak corresponding to 2-(biphenyl-4-yl)propionic acid is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.5%), the area of any other *secondary peak* is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.2%) and the sum of the areas of any *secondary peaks* is not greater than five times the area of the peak in the chromatogram obtained with solution (2) (1%).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of flurbiprofen with 60 mL of 0.1M *sodium hydroxide* for 5 minutes, dilute to 100 mL with 0.1M *sodium hydroxide*, filter if necessary and dilute 10 mL of the filtrate to 100 mL with the same solvent. Further dilute 10 mL to 100 mL with the same solvent and measure the *absorbance* of the resulting solution at the maximum at 247 nm, Appendix II B. Calculate the content of $C_{15}H_{13}FO_2$ taking 802 as the value of A(1%, 1 cm) at the maximum at 247 nm.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

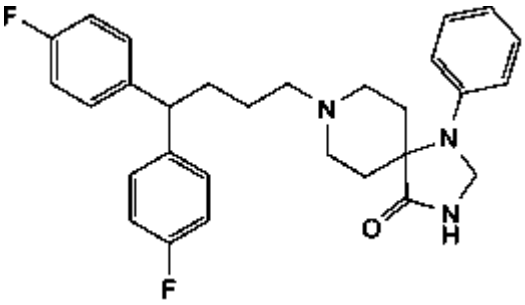
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluspirilene

General Notices

(Ph. Eur. monograph 1723)



$C_{29}H_{31}F_2N_3O$ 475.6 *1841-19-6*

Action and use

Antipsychotic.

Ph Eur

DEFINITION

8-[4,4-bis(4-Fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *fluspirilene CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methylene chloride R*, gently evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.25 g in 25 mL of *methylene chloride R*.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in *dimethylformamide R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *fluspirilene impurity C CRS* in *dimethylformamide R*, add 0.5 mL of the test solution and dilute to 100.0 mL with *dimethylformamide R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with *dimethylformamide R*. Dilute 1.0 mL of this solution to 25.0 mL with *dimethylformamide R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm,

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

— *mobile phase A*: 13.6 g/L solution of *tetrabutylammonium hydrogen sulfate R*,

— *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	75 → 70	25 → 30
15 - 20	70	30
20 - 22	70 → 0	30 → 100
22 - 30	0	100

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to fluspirilene (retention time = about 15 min): impurity A = about 0.8; impurity B = about 0.93; impurity C = about 0.97.

System suitability Reference solution (a):

— *resolution*: minimum 2.2 between the peaks due to impurity C and fluspirilene.

Limits:

— *impurities A, B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent),

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent),

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.350 g in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 47.56 mg of $C_{29}H_{31}F_2N_3O$.

STORAGE

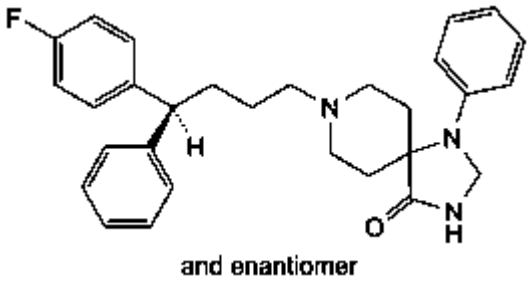
Protected from light.

IMPURITIES

www.webofpharma.com

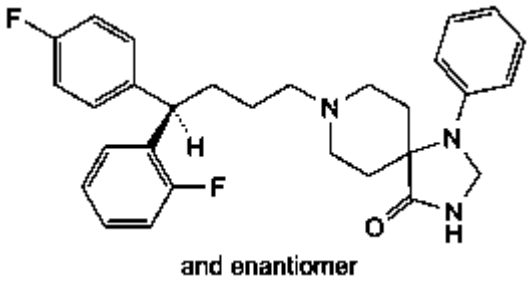
https://thuocngocanh.com/

Specified impurities *A, B, C.*



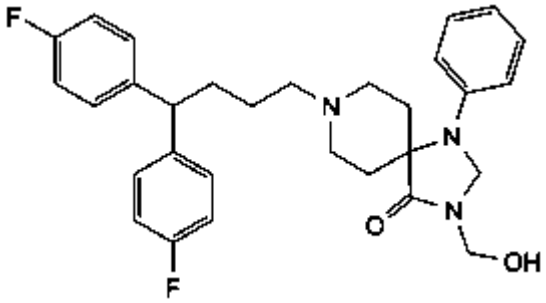
and enantiomer

A. 8-[(4*RS*)-4-(4-fluorophenyl)-4-phenylbutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one,



and enantiomer

B. 8-[(4*RS*)-4-(2-fluorophenyl)-4-(4-fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one,



C. 8-[4,4-bis(4-fluorophenyl)butyl]-3-(hydroxymethyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

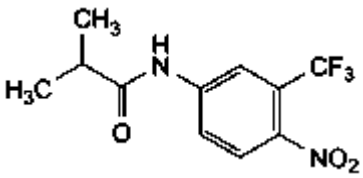
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flutamide

General Notices

(Ph. Eur. monograph 1423)



$C_{11}H_{11}F_3N_2O_3$ 276.2 *13311-84-7*

Action and use

Antiandrogen.

Ph Eur

DEFINITION

2-Methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone and in ethanol (96 per cent), practically insoluble in heptane.

mp

About 112 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *flutamide CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of *flutamide for system suitability CRS* (containing impurities A, B and C) in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 20.0 mg of *flutamide CRS* in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *water R* (50:50 *V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 1.5 times the retention time of flutamide.

Identification of impurities Use the chromatogram supplied with *flutamide for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention With reference to flutamide (retention time = about 19 min): impurity B = about 0.5; impurity A = about 0.6; impurity C = about 0.7.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities B and A.

Calculation of percentage contents:

— for each impurity, use the concentration of flutamide in reference solution (b).

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurities A, B, C*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{11}H_{11}F_3N_2O_3$ taking into account the assigned content of *flutamide CRS*.

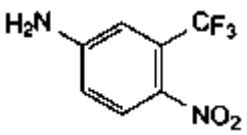
STORAGE

Protected from light.

IMPURITIES

Specified impurities *A, B, C.*

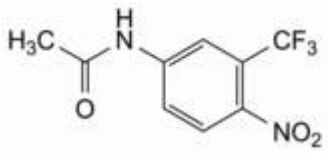
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, F.*



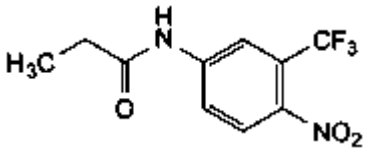
A. 4-nitro-3-(trifluoromethyl)aniline,

www.webofpharma.com

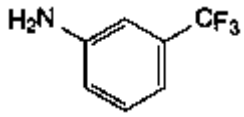
https://thuocngocanh.com/



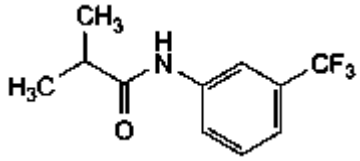
B. *N*-[4-nitro-3-(trifluoromethyl)phenyl]acetamide,



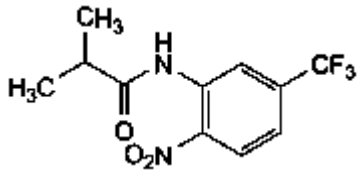
C. *N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide,



D. 3-(trifluoromethyl)aniline,



E. 2-methyl-*N*-[3-(trifluoromethyl)phenyl]propanamide,



F. 2-methyl-*N*-[2-nitro-5-(trifluoromethyl)phenyl]propanamide.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone and Salmeterol Inhalation Powder

General Notices

Fluticasone and Salmeterol Inhalation Powder, metered-dose.

Action and use

Glucocorticoid and beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Fluticasone and Salmeterol Inhalation Powder consists of Fluticasone Propionate and Salmeterol Xinafoate either alone or combined with a suitable carrier. It is administered by a device-metered dry-powder inhaler.

The inhalation complies with the requirements stated under Preparations for Inhalation and with the following requirements..

PRODUCTION

The size of particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

94.0 to 107.5% of the stated amount.

Content of salmeterol, $C_{25}H_{37}NO_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 300 nm of solution (2) obtained in the test for Uniformity of delivered dose closely resembles that of a solution containing 0.00005% w/v of *salmeterol xinafoate BPCRS* and an appropriate concentration of *fluticasone propionate BPCRS* in *methanol (70%)*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to fluticasone propionate in the chromatogram obtained with solution (3). The chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to salmeterol in the chromatogram obtained with solution (3).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Uniformity of delivered dose

Complies with the requirements stated under Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol (70%)* to produce a solution containing 0.00025% w/v of Fluticasone Propionate.

(2) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol (70%)* to produce a solution containing the equivalent of 0.00005% w/v of salmeterol.

(3) 0.00025% w/v of *fluticasone propionate BPCRS* and 0.00007% w/v of *salmeterol xinafoate BPCRS* in *methanol (70%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm and a fluorimetric detector with an excitation wavelength of 225 nm and an emission wavelength of 305 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile*, 30 volumes of *methanol* and 40 volumes of a solution containing 0.2M *ammonium acetate* and 0.5% w/v of *tetrabutylammonium hydrogen sulfate* in *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time of salmeterol is about 4 minutes and the retention time of fluticasone propionate is about 9 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to salmeterol and fluticasone propionate is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$, per delivered dose using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS* at 239 nm.

Calculate the content of salmeterol, $C_{25}H_{37}NO_4$, per delivered dose using the declared content of $C_{25}H_{37}NO_4$ in *salmeterol xinafoate BPCRS* using fluorimetric detection.

Repeat the procedure as described for reservoir systems under Inhalation powders, Uniformity of delivered dose.

www.webofpharma.com

https://thuocngocanh.com/

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A.

Solution A 30 volumes of *water* and 70 volumes of a solution containing 0.05% v/v of *orthophosphoric acid* in *methanol*.

(1) Dissolve, with the aid of ultrasound, a quantity of the powder in sufficient solution A to produce a solution containing 0.02% w/v of Fluticasone Propionate.
(2) Dissolve, with the aid of ultrasound, a quantity of the powder in sufficient solution A to produce a solution containing the equivalent of 0.01% w/v of salmeterol.
(3) Dilute 1 volumes of solution (1) to 50 volumes. Further dilute 1 volume of the resulting solution to 10 volumes.
(4) 0.00036% w/v of *salmeterol xinafoate impurity 1 BPCRS*.
(5) 0.02% w/v of *fluticasone propionate BPCRS* and 0.00006% w/v of *fluticasone impurity D EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Inertsil ODS2 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 228 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05M *ammonium dihydrogen orthophosphate* adjusted to pH 2.9 with 10% v/v of *orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	70	30	isocratic
1-61	70→22	30→78	linear gradient
61-62	22→70	78→30	linear gradient
62-71	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to fluticasone propionate (retention time about 37 minutes) are:

Name	Relative retention time
Salmeterol Xinafoate impurity A	0.14
Salmeterol Xinafoate impurity B	0.25

www.webofpharma.com

https://thuocngocanh.com/

Salmeterol Xinafoate impurity C	0.32
Salmeterol Xinafoate impurity E	0.37
Fluticasone Propionate impurity 1	0.38
Salmeterol	0.41
Xinafoate	0.50
Fluticasone Propionate impurity A	0.59
Fluticasone Propionate impurity B	0.67
Salmeterol Xinafoate impurity G	0.71
Fluticasone Propionate impurity 2	0.87
Fluticasone Propionate impurity C	0.89
Fluticasone Propionate impurity 3	0.90
Fluticasone Propionate impurity D	0.97
Fluticasone Propionate impurity E	1.05
Fluticasone Propionate impurity F	1.08
Fluticasone Propionate impurity G	1.09
Fluticasone Propionate impurity H	1.48

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.5.

LIMITS

Calculate all unspecified impurities relative to fluticasone propionate.

For fluticasone propionate In the chromatogram obtained with solution (1):

the area of any peak corresponding to Fluticasone Propionate impurity D or G is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (3) (1.2%).

Disregard any peak:

www.webofpharma.com

https://thuocngocanh.com/

due to salmeterol or related impurities;

with an area less than half the area of the peak due to fluticasone in the chromatogram obtained with solution (3) (0.1%).

For salmeterol In the chromatogram obtained with solution (2):

the area of any peak corresponding to Salmeterol impurity 1 is not greater than the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (2.5%);

the area of any peak corresponding to Salmeterol impurity A, B, C, E or G, is not greater than 0.2 times the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (0.5% of each);

the sum of the areas of any peak corresponding to Salmeterol impurity 1 and impurities A, B, C, E or G is not greater than twice the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (5%).

ASSAY

For fluticasone propionate Use the average of the individual results obtained in the test for Uniformity of delivered dose.
For salmeterol Use the average of the individual results obtained in the test for Uniformity of delivered dose.

LABELLING

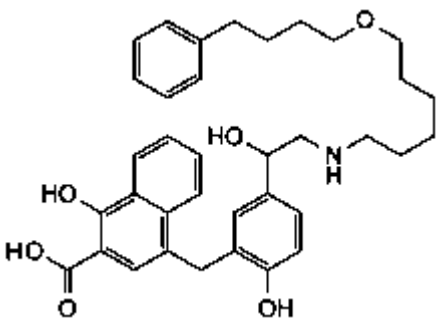
The quantity of Salmeterol Xinafoate is stated in terms of the equivalent amount of salmeterol.

IMPURITIES

The impurities limited by the requirements of this monograph include:

A, C, D, E, F, G and H listed under Fluticasone Propionate;

A, B, C, E and G listed under Salmeterol Xinafoate;



1. *rac*-1-hydroxy-4-{[2-hydroxy-5-(1-hydroxy-2-{6-(4-phenylbutoxy)hexyl]amino}ethyl)phenyl]methyl}naphthalene-2-carboxylic acid

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products
Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone and Salmeterol Inhalation Powder, pre-metered

General Notices

Fluticasone and Salmeterol Inhalation Powder, pre-dispensed

Action and use

Glucocorticoid and beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Fluticasone and Salmeterol Inhalation Powder, pre-metered consists of Fluticasone Propionate and Salmeterol Xinafoate in *microfine powder* either alone or combined with a suitable carrier. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, pre-metered complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7, Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

94.0 to 107.5% of the stated amount.

Content of salmeterol, $C_{25}H_{37}NO_4$

92.5 to 107.5% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 300 nm of solution (2) obtained in the test for Uniformity of delivered dose closely resembles that of a solution containing 0.00005% w/v of *salmeterol xinafoate BPCRS* and an appropriate concentration of *fluticasone propionate BPCRS* in *methanol (70%)*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to fluticasone propionate in the chromatogram obtained with solution (3), and the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to salmeterol in the chromatogram obtained with solution (3).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol (70%)* to produce a solution containing 0.00025% w/v of Fluticasone Propionate.

(2) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol (70%)* to produce a solution containing the equivalent of 0.00005% w/v of salmeterol.

(3) 0.00025% w/v of *fluticasone propionate BPCRS* and 0.00007% w/v of *salmeterol xinafoate BPCRS* in *methanol (70%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm and a fluorimetric detector with an excitation wavelength of 225 nm and an emission wavelength of 305 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile*, 30 volumes of *methanol* and 40 volumes of a solution containing 0.2M *ammonium acetate* and 0.5% w/v of *tetrabutylammonium hydrogen sulfate* in *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of salmeterol is about 4 minutes and the retention time of fluticasone propionate is about 9 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to salmeterol and fluticasone propionate is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$, per delivered dose using the declared content of $C_{25}H_{31}F_3O_5S$, in *fluticasone propionate BPCRS* at 239 nm.

Calculate the content of salmeterol, $C_{25}H_{37}NO_4$, per delivered dose using the declared content of $C_{25}H_{37}NO_4$ in *salmeterol xinafoate BPCRS* using fluorimetric detection.

Repeat the procedure as described for pre-metered systems under Powders for Inhalation, Uniformity of delivered dose.

Related substances

www.webofpharma.com

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A.

Solution A 30 volumes of *water* and 70 volumes of a solution containing 0.05% v/v of *orthophosphoric acid* in *methanol*.

(1) Dissolve, with the aid of ultrasound, a quantity of the powder in sufficient solution A to produce a solution containing 0.02% w/v of Fluticasone Propionate.

(2) Dissolve, with the aid of ultrasound, a quantity of the powder in sufficient solution A to produce a solution containing the equivalent of 0.01% w/v of salmeterol.

(3) Dilute 2 volumes of solution (1) to 100 volumes. Further dilute 1 volume of the resulting solution to 10 volumes.

(4) 0.00036% w/v of *salmeterol xinafoate impurity 1 BPCRS*.

(5) 0.000015% w/v of *salmeterol xinafoate impurity 1 BPCRS*.

(6) 0.02% w/v of *fluticasone propionate BPCRS* and 0.00006% w/v of *fluticasone impurity D EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5 µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 228 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05M *ammonium dihydrogen orthophosphate* adjusted to pH 2.9 with 10% v/v of *orthophosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	70	30	isocratic
1-61	70→22	30→78	linear gradient
61-62	22→70	78→30	linear gradient
62-71	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to fluticasone propionate (retention time about 37 minutes) are: salmeterol, about 0.41; impurity 1, about 0.74; fluticasone impurity D, about 0.97 and fluticasone propionate impurity G, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6), the *resolution* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.5.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

For fluticasone propionate In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D and any peak corresponding to impurity G is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (3) (1.2%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

For salmeterol In the chromatogram obtained with solution (2):

the area of any peak corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than ten times the area of the principal peak in the chromatogram obtained with solution (5) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder the contents of 20 pre-dispensed units. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol (70%)*.

(1) Dissolve, with the aid of ultrasound, a quantity of the powder to produce a solution containing 0.002% w/v of Fluticasone Propionate.
(2) Dissolve, with the aid of ultrasound, a quantity of the powder to produce a solution containing the equivalent of 0.0004% w/v of salmeterol.
(3) 0.002% w/v of *fluticasone propionate BPCRS* and 0.00058% w/v of *salmeterol xinafoate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of delivered dose may be used with an injection volume of 50 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to salmeterol and fluticasone propionate is at least 6.0.

DETERMINATION OF CONTENT

In the chromatogram obtained with solution (1) at 239 nm; calculate the content of $C_{25}H_{31}F_3O_5S$ in the powder using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (2) using fluorimetric detection; calculate the content of $C_{25}H_{37}NO_4$ in the powder using the declared content of $C_{25}H_{37}NO_4$ in *salmeterol xinafoate BPCRS*.

LABELLING

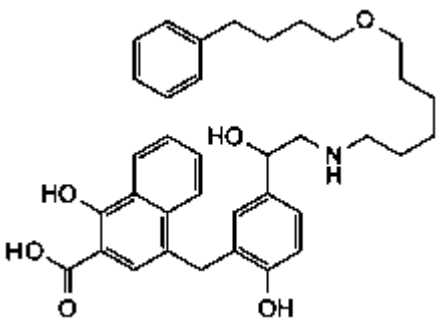
The quantity of Salmeterol Xinafoate is stated in terms of the equivalent amount of salmeterol.

IMPURITIES

The impurities limited by the requirements of this monograph include:

A, C, D, E, F, G and H listed under Fluticasone Propionate;

A, B, C, E and G listed under Salmeterol Xinafoate;



1. *rac*-1-hydroxy-4-{[2-hydroxy-5-(1-hydroxy-2-{6-(4-phenylbutoxy)hexyl]amino}ethyl)phenyl]methyl}naphthalene-2-carboxylic acid

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone and Salmeterol Pressurised Inhalation, Suspension

General Notices

Action and use

Glucocorticoid and beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Fluticasone and Salmeterol Pressurised Inhalation, Suspension is a suspension of Fluticasone Propionate and Salmeterol Xinafoate in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7, Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

85.0 to 115.0% of the stated dose.

Content of salmeterol, $C_{25}H_{37}NO_4$

85.0 to 115.0% of the stated dose.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 300 nm of solution (2) obtained in the test for Uniformity of delivered dose closely resembles that of a solution containing 0.000025% w/v of *salmeterol xinafoate BPCRS* and an appropriate concentration of *fluticasone propionate BPCRS*, depending on the strength of the product, in a mixture of *methanol (70%)*.

B. In the test for Uniformity of delivered dose, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to fluticasone propionate in the chromatogram obtained with solution (3).

C. In the test for Uniformity of delivered dose, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to salmeterol in the chromatogram obtained with solution (3).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Uniformity of delivered dose

Complies with the requirements stated under Pressurised Metered-dose Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol (70%)* to produce a solution containing 0.000125% w/v of Fluticasone Propionate.

(2) Collect single doses of the preparation being examined using the procedure described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol (70%)* to produce a solution containing the equivalent of 0.000025% w/v of salmeterol.

(3) 0.000125% w/v of *fluticasone propionate BPCRS* and 0.000036% w/v of *salmeterol xinafoate BPCRS* in *methanol (70%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5 µm) (Hypersil BDS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm and a fluorimetric detector with an excitation wavelength of 225 nm and an emission wavelength of 305 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile*, 30 volumes of *methanol* and 40 volumes of a solution containing 0.2M *ammonium acetate* and 0.5% w/v of *tetrabutylammonium hydrogen sulfate* in *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of salmeterol is about 4 minutes and the retention time of fluticasone propionate is about 9 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks dues to salmeterol and fluticasone propionate is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$, per delivered dose using the declared content of $C_{25}H_{31}F_3O_5S$, in *fluticasone propionate BPCRS* at 239 nm.

Calculate the content of salmeterol, $C_{25}H_{37}NO_4$, per delivered dose using the declared content of $C_{25}H_{37}NO_4$ in *salmeterol xinafoate BPCRS* using fluorimetric detection.

Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution A.

www.webofpharma.com

https://thuocngocanh.com/

Solution A 0.5 volume of *orthophosphoric acid*, 300 volumes of *water* and 700 volumes of *methanol*.

(1) Dissolve with the aid of ultrasound, a quantity of the suspension containing 2 mg of Fluticasone Propionate in 7 mL of 0.05% v/v of *orthophosphoric acid* in *methanol*. Add 3 mL of *water* and mix for a further 5 minutes.

(2) Dissolve with the aid of ultrasound, a quantity of the suspension containing the equivalent of 1 mg of salmeterol in 7 mL of 0.05% v/v of *orthophosphoric acid* in *methanol*. Add 3 mL of *water* and mix for a further 5 minutes.

(3) Dilute 2 volumes of solution (1) to 100 volumes with solution A. Further dilute 1 volume of the resulting solution to 10 volumes with solution A.

(4) Dilute 2 volumes of solution (2) to 100 volumes with solution A. Further dilute 1 volume of the resulting solution to 10 volumes with solution A.

(5) 0.005% w/v of *fluticasone propionate BPCRS* and 0.00002% w/v of *fluticasone impurity D EPCRS* in *methanol (70%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5 µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 228 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 30 volumes of *acetonitrile* and 70 volumes of 0.05M *ammonium dihydrogen orthophosphate*, previously adjusted to pH 2.9 with 10% v/v of *orthophosphoric acid*.

Mobile phase B 22 volumes of 0.05M *ammonium dihydrogen orthophosphate*, previously adjusted to pH 2.9 with 10% v/v of *orthophosphoric acid* and 78 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-60	100→0	0→100	linear gradient
60-61	0→100	100→0	linear gradient
61-70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the relative retention with respect to fluticasone propionate (retention time about 37 minutes) are:

Name	Relative retention time
Salmeterol Xinafoate impurity A	0.14
Salmeterol Xinafoate impurity B	0.25
Salmeterol Xinafoate impurity C	0.32

www.webofpharma.com

https://thuocngocanh.com/

Salmeterol Xinafoate impurity E	0.37
Fluticasone Propionate impurity 1	0.38
Salmeterol	0.41
Xinafoate	0.50
Fluticasone Propionate impurity A	0.59
Fluticasone Propionate impurity B	0.67
Salmeterol Xinafoate impurity G	0.71
Fluticasone Propionate impurity 2	0.87
Fluticasone Propionate impurity C	0.89
Fluticasone Propionate impurity 3	0.90
Fluticasone Propionate impurity D	0.97
Fluticasone Propionate impurity E	1.05
Fluticasone Propionate impurity F	1.08
Fluticasone Propionate impurity G	1.09
Fluticasone Propionate impurity H	1.48

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.5.

LIMITS

Calculate all unspecified impurities relative to fluticasone propionate.

For fluticasone propionate In the chromatogram obtained with solution (1):

the area of any peak corresponding to Fluticasone impurity D or G is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3% of each);

the area of any other *secondary peak* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (3) (1.5%).

Disregard any peak:

due to salmeterol or related impurities;

www.webofpharma.com

https://thuocngocanh.com/

with an area less than half the area of the peak due to fluticasone in the chromatogram obtained with solution (3) (0.1%).

For salmeterol In the chromatogram obtained with solution (2):

the area of any peak corresponding to Salmeterol Xinafoate A, B, C, E or G is not greater than 2.5 times the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (0.5% of each);

the sum of the areas of any peak corresponding to Salmeterol Xinafoate A, B, C, E or G is not greater than 7.5 times the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (1.5%).

Disregard any peak corresponding to Salmeterol Xinafoate A, B, C, E or G with an area less than half the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (0.1%).

ASSAY

For fluticasone propionate

Use the average of the individual results obtained in the test for Uniformity of delivered dose.

For salmeterol

Use the average of the individual results obtained in the test for Uniformity of delivered dose.

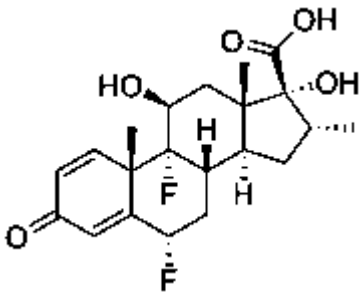
LABELLING

The label states the content of fluticasone propionate and salmeterol in terms of the equivalent metered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include:

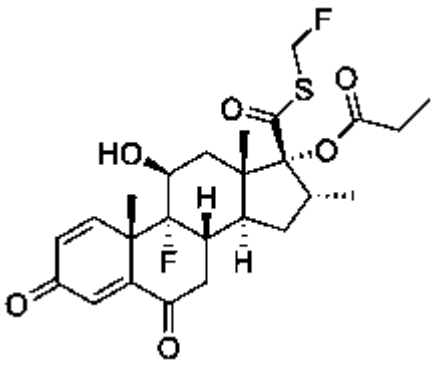
A, B, C, D, E, F, G and H listed under Fluticasone Propionate and A, B, C, E and G listed under Salmeterol Xinafoate.



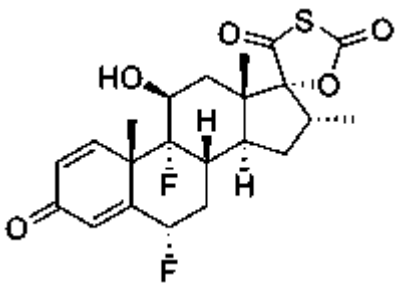
1. 6α,9-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrost-1,4-diene-17β-carboxylic acid

www.webofpharma.com

https://thuocngocanh.com/



2. 6α,9-Difluoro-17β-[(fluoromethyl)sulfanylcarbonyl]-11β-hydroxy-16α-methyl-3,6-dioxoandrostandrost1,4-dien-17α-yl propanoate



3. (17*R*)-6α,9-Difluoro-11β-hydroxy-16α-methyl-2′,3,4′-trioxospiro[androsta-1,4-diene-17,5′-[1,3]oxathiolane]

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Cream

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluticasone Cream contains Fluticasone Propionate in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Transfer a quantity of the cream containing 1 mg of Fluticasone Propionate to a separating funnel, add 25 mL of *acetonitrile* and 25 mL of *n-hexane*, shake for 3 minutes and allow to separate. Filter the lower layer through an absorbent cotton plug, previously washed with *acetonitrile*, into a 50-mL graduated flask, repeat the extraction with one 5-mL and then one 2-mL quantity of *acetonitrile*, filter and add the extracts to the filtered layer; wash the absorbent cotton plug with 1 to 2 mL of *acetonitrile*, add the washings to the filtered layer and dilute the combined extracts to 50 mL with *acetonitrile*. Evaporate 4 mL of the resulting solution to dryness using a rotary evaporator at a temperature of 40° and dissolve the residue in 0.2 mL of *acetonitrile*.

(2) 0.04% w/v of *fluticasone propionate BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel F_{254}* precoated plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 40 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry it in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 8 volumes of *ethyl acetate* and 30 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Transfer a quantity of the cream containing 1 mg of Fluticasone Propionate to a separating funnel, add 25 mL of *ethanol (65%)*, stopper and shake until the cream is completely dispersed. Add 25 mL of *n-hexane*, shake for 3 minutes and allow to separate, filter the lower aqueous layer through an absorbent cotton plug, previously washed with *ethanol (65%)*, into a graduated flask and repeat the extraction with one 5-mL and then one 2-mL quantity of *ethanol (65%)*, filtering the aqueous ethanol extracts into the same graduated flask. Wash the absorbent cotton plug with *ethanol (65%)*, collecting the washings in the flask and dilute the combined extracts to 50 mL with *ethanol (65%)*.

(2) 0.002% w/v of *fluticasone propionate BPCRS* in *methanol (80%)*.

(3) 0.0004% w/v of *fluticasone impurity D EPCRS* and 0.002% w/v of *fluticasone propionate BPCRS* in *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile*, 35 volumes of 0.01M *ammonium dihydrogen orthophosphate* previously adjusted to pH 3.5 with *orthophosphoric acid* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.6. If necessary, adjust the proportion of *acetonitrile* in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{31}F_3O_5S$ in the cream using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

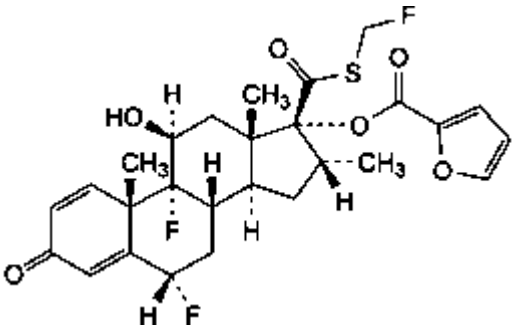
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Furoate

General Notices

(Ph. Eur. monograph 2768)



$C_{27}H_{29}F_3O_6S$ 538.6 *397864-44-7*

Action and use

Glucocorticoid.

Ph Eur

DEFINITION

6α,9-Difluoro-17β-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, slightly soluble to practically insoluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *fluticasone furoate CRS*.

TESTS

Related substances

A. Liquid chromatography (*2.2.29*). *Protect the solutions from light*.

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in 50 mL of *acetonitrile R* using sonication until complete dissolution, add about 48 mL of *water R*, mix, allow to equilibrate at room temperature and dilute to 100.0 mL with *water R*.

Reference solution (a) Dissolve 25.0 mg of *fluticasone furoate CRS* in 50 mL of *acetonitrile R* using sonication until complete dissolution, add about 48 mL of *water R*, mix, allow to equilibrate at room temperature and dilute to 100.0 mL with *water R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2.5 mg of *fluticasone furoate for peak identification CRS* (containing impurities A, B and K) in 5 mL of *acetonitrile R* using sonication until complete dissolution and dilute to 10 mL with *water R*.

Reference solution (d) Dissolve 2.5 mg of *fluticasone furoate for system suitability CRS* (containing impurity F) in 5 mL of *acetonitrile R* using sonication until complete dissolution and dilute to 10 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: *methanol R1*, *acetonitrile for chromatography R*, 0.1 per cent *V/V* solution of *trifluoroacetic acid R* (10:30:60 *V/V/V*);

— *mobile phase B*: *methanol R1*, *acetonitrile for chromatography R* (25:75 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 32	100 → 33	0 → 67

Flow rate 1.5 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 245 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use chromatogram A supplied with *fluticasone furoate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and K; use chromatogram A supplied with *fluticasone furoate for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to fluticasone furoate (retention time = about 15 min): impurity A = about 0.6; impurity B = about 0.8; impurities E, F and G = about 1.1; impurity K = about 1.3.

System suitability Reference solution (d):

— *resolution*: minimum 4.0 between the peaks due to fluticasone furoate and impurity F.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.6; impurity K = 1.7;

— for each impurity, use the concentration of fluticasone furoate in reference solution (b).

Limits:

— *impurity K*: maximum 0.3 per cent;

— *impurities A, B*: for each impurity, maximum 0.15 per cent;

— *sum of impurities E, F and G*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

B. *Perform test B only in cases where, in test A, any peak with a relative retention of about 1.1 and/or 1.16 exceeds the prescribed limits.* Liquid chromatography (2.2.29) as described in test A for related substances with the following modifications.

Column:

— *temperature*: 55 °C.

Mobile phase Mix 18 volumes of *tetrahydrofuran R*, 28 volumes of *methanol R1* and 54 volumes of *water for chromatography R* and add 0.05 volumes of *trifluoroacetic acid R*.

Flow rate 1.3 mL/min.

Run time 3.5 times the retention time of fluticasone furoate.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use chromatogram B supplied with *fluticasone furoate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and K; use chromatogram B supplied with *fluticasone furoate for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity F.

Relative retention With reference to fluticasone furoate (retention time = about 14 min): impurity F = about 1.1.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to fluticasone furoate and impurity F.

Calculation of percentage contents:

— for each impurity, use the concentration of fluticasone furoate in reference solution (b).

Limits:

— *any impurity*: for each impurity, maximum 0.10 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peaks due to impurities A, B and K.

Water (*2.5.32*)

Maximum 0.2 per cent, determined on 0.100 g using the evaporation technique at 110 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{27}H_{29}F_3O_6S$ taking into account the assigned content of *fluticasone furoate CRS*.

STORAGE

Protected from light.

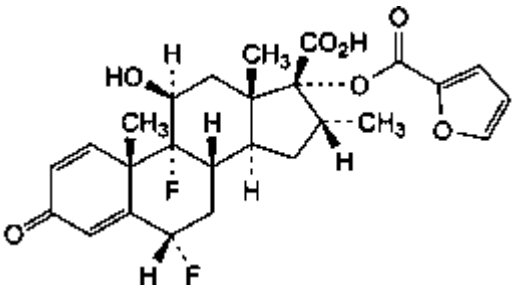
IMPURITIES

Specified impurities *A, B, E, F, G, K.*

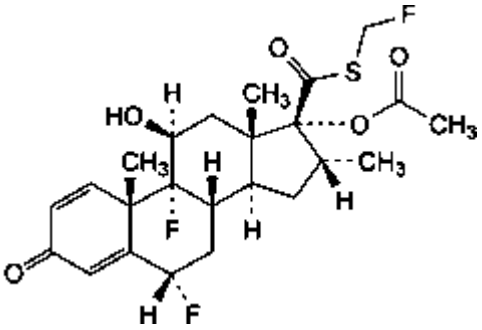
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H, I, J, L.*

www.webofpharma.com

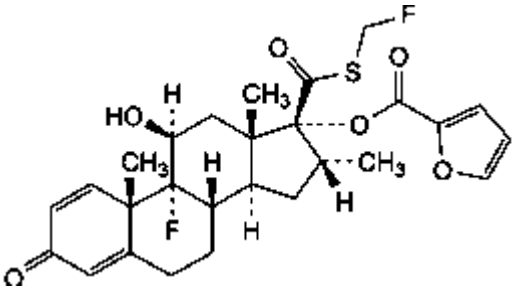
https://thuocngocanh.com/



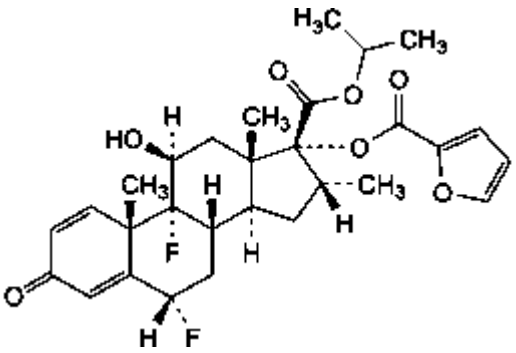
A. 6α,9-difluoro-17α-[(furan-2-carbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid,



B. 6α,9-difluoro-17β-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl acetate (fluticasone propionate impurity C),



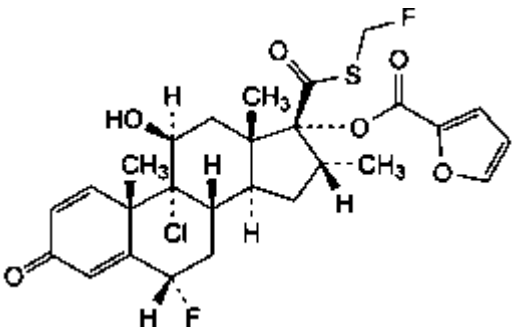
E. 9-fluoro-17β-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate,



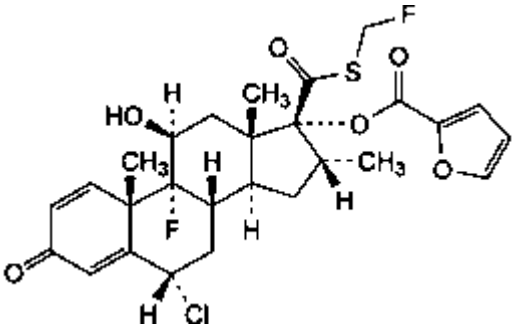
F. propan-2-yl 6α,9-difluoro-17α-[(furan-2-carbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate,

www.webofpharma.com

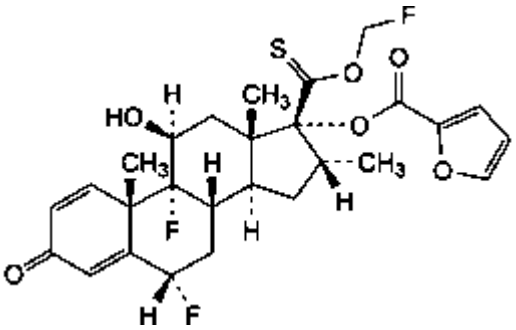
https://thuocngocanh.com/



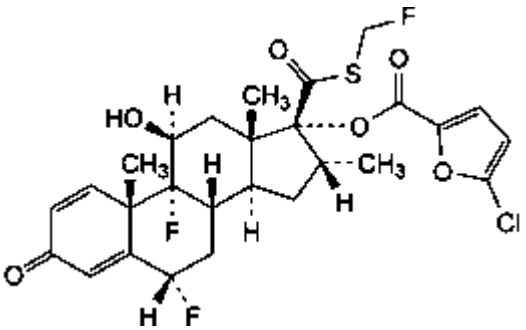
G. 9-chloro-6α-fluoro-17β-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate,



H. 6α-chloro-9-fluoro-17β-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate,



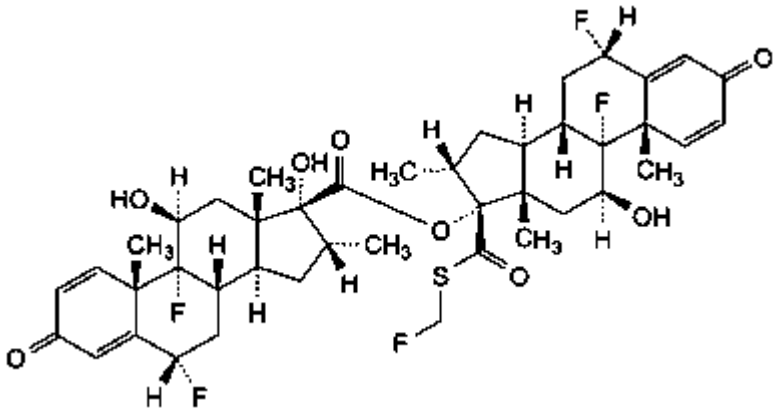
I. 6α,9-difluoro-17β-[(fluoromethoxy)carbonothioyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate,



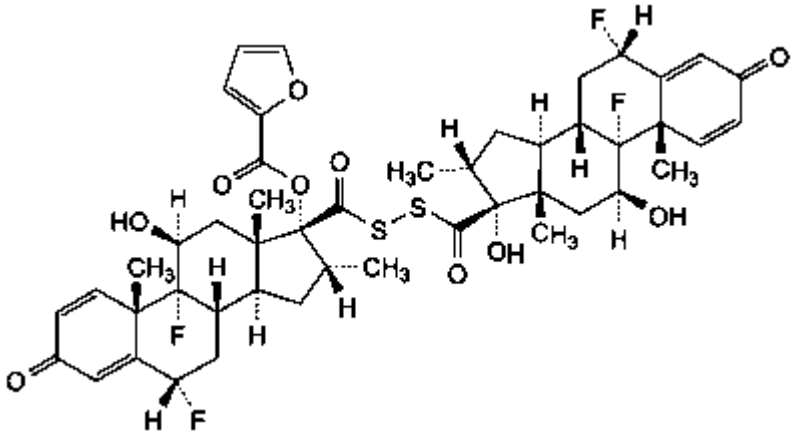
J. 6α,9-difluoro-17β-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl 5-chlorofuran-2-carboxylate,

www.webofpharma.com

https://thuocngocanh.com/



K. 6α,9-difluoro-17β-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl 6α,9-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate (fluticasone propionate impurity G),



L. 6α,9-difluoro-17α-[(furan-2-carbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic 6α,9-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17β-carboxylic dithioperoxyanhydride.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Inhalation Powder

General Notices

Fluticasone Powder for Inhalation, metered-dose powder inhaler

Action and use

Glucocorticoid.

DEFINITION

Fluticasone Inhalation Powder consists of Fluticasone Propionate in *microfine powder* either alone or combined with a suitable carrier. It is administered by a dry-powder inhaler.

The inhalation powder complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

80.0 to 120.0% of the stated amount.

IDENTIFICATION

A. Dilute a quantity of the inhalation powder in a mixture of 2 volumes of *water* and 8 volumes of *methanol* to produce a solution expected to contain 0.0005% w/v of Fluticasone Propionate. The light absorption, Appendix II B, in the range 210 to 300 nm closely resembles that of a solution containing 0.0005% w/v of *fluticasone propionate BPCRS* in solvent A and exhibits a single maximum at 240 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 35 volumes of *water* and 65 volumes of *methanol* (solvent A).

www.webofpharma.com

https://thuocngocanh.com/

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient of solvent A to produce a solution expected to contain 0.0005% w/v of Fluticasone Propionate.

(2) 0.0005% w/v of *fluticasone propionate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile*, 35 volumes of 0.01M *ammonium dihydrogen orthophosphate* and 50 volumes of *methanol* adjusted to pH 3.5 with *orthophosphoric acid* or *dilute ammonia*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the principal peak is not greater than 2.5.

DETERMINATION OF CONTENT

Calculate the content of Fluticasone Propionate, $C_{25}H_{31}F_3O_5S$, per delivered dose using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS*. Repeat the procedure as described for reservoir systems under Inhalation Powders, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the inhalation powder containing 0.5 mg of Fluticasone Propionate in 10 mL of a mixture of 7 volumes of *acetonitrile*, 20 volumes of *water* and 23 volumes of *methanol* and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes in a mixture of equal volumes of *acetonitrile* and *water*.

(3) 0.0004% w/v of *fluticasone impurity D EPCRS* and 0.002% w/v of *fluticasone propionate BPCRS* in a mixture of equal volumes of *acetonitrile* and *water*.

(4) Dilute 1 volume of solution (2) to 5 volumes in a mixture of equal volumes of *acetonitrile* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 23 volumes of *acetonitrile* and 77 volumes of *methanol*.

Mobile phase B 0.01M *ammonium dihydrogen orthophosphate*, adjusted to pH 3.5 with *acetic acid* or *dilute ammonia*.

Equilibrate the column with a mobile phase ratio A:B of 60:40. Inject solutions (1) and (3) and start the elution isocratically with the chosen mobile phase. One minute after elution of the apex of the fluticasone propionate peak start a linear gradient elution to reach a mobile phase ratio A:B of 85:15 over a period of 10 minutes. Continue the chromatography for 10 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fluticasone propionate and fluticasone impurity D is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Inhalation Powder, pre-metered

General Notices

Fluticasone Powder for Inhalation, pre-dispensed

Action and use

Glucocorticoid.

DEFINITION

Fluticasone Inhalation Powder, pre-metered consists of Fluticasone Propionate in *microfine powder* either alone or combined with a suitable carrier. The blister is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, pre-metered complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

80.0 to 120.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 300 nm of the final solution obtained in the test for Uniformity of delivered dose closely resembles that of a solution containing 0.0005% w/v of *fluticasone propionate BPCRS* in solvent A and exhibits a single maximum at 240 nm.

B. In the test for Uniformity of delivered dose, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Uniformity of delivered dose

www.webofpharma.com

https://thuocngocanh.com/

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 35 volumes of *water* and 65 volumes of *methanol* (solvent A).

(1) Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient of solvent A to produce a solution expected to contain 0.0005% w/v of Fluticasone Propionate.

(2) 0.0005% w/v of *fluticasone propionate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile*, 35 volumes of 0.01M *ammonium dihydrogen orthophosphate* and 50 volumes of *methanol* adjusted to pH 3.5 with *orthophosphoric acid* or *dilute ammonia*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the principal peak is not greater than 2.5.

DETERMINATION OF CONTENT

Calculate the content of Fluticasone Propionate, $C_{25}H_{31}F_3O_5S$, per delivered dose using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS*. Repeat the procedure as described for pre-metered systems under Inhalation Powders, Uniformity of delivered dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powder, containing 0.5 mg of Fluticasone Propionate in 10 mL of a mixture of 7 volumes of *acetonitrile*, 20 volumes of *water* and 23 volumes of *methanol* and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes in equal volumes of *acetonitrile* and *water*.

(3) 0.0004% w/v of *fluticasone impurity D EPCRS* and 0.002% w/v of *fluticasone propionate BPCRS* in equal volumes of *acetonitrile* and *water*.

(4) Dilute 1 volume of solution (2) to 5 volumes in equal volumes of *acetonitrile* and *water*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 23 volumes of *acetonitrile* and 77 volumes of *methanol*.

Mobile phase B 0.01M *ammonium dihydrogen orthophosphate*, adjusted to pH 3.5 with *acetic acid* or *dilute ammonia*.

Equilibrate the column with a mobile phase ratio A:B of 60:40. Inject solutions (1) and (3) and start the elution isocratically with the chosen mobile phase. One minute after elution of the apex of the fluticasone propionate peak start a linear gradient elution to reach a mobile phase ratio A:B of 85:15 over a period of 10 minutes. Continue the chromatography for 10 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to fluticasone propionate and fluticasone impurity D is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Nasal Drops

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluticasone Nasal Drops are a suspension of Fluticasone Propionate in a suitable liquid in a container fitted with an appropriate nasal delivery system.

The nasal drops comply with the requirements stated under Nasal Preparations and with the following requirements.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

95.0 to 110.0% of the stated amount.

Carry out all the following procedures in the dark or under long-wavelength light (greater than 420 nm). Prepare solutions immediately before use and protect them from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the nasal drops containing 2 mg of Fluticasone Propionate add sufficient *acetonitrile* to produce 5 mL, shake for 3 minutes and filter.

(2) 0.04% w/v of *fluticasone propionate BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 40 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, allow it to dry in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 8 volumes of *ethyl acetate* and 30 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the nasal drops containing 1 mg of Fluticasone Propionate to 5 mL with a mixture of equal volumes of mobile phase A and mobile phase B and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with a mixture of equal volumes of mobile phase A and mobile phase B.
(3) 0.02% w/v of *fluticasone propionate BPCRS* and 0.00004% w/v of *fluticasone impurity D EPCRS* in a mixture of equal volumes of mobile phase A and mobile phase B.
(4) Dilute 1 volume of solution (2) to 10 volumes with a mixture of equal volumes of mobile phase A and mobile phase B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A A solution containing 0.05% v/v of *orthophosphoric acid* and 3.0% v/v of *methanol* in *acetonitrile*.

Mobile phase B A solution containing 0.05% v/v of *orthophosphoric acid* and 3.0% v/v of *methanol* in *water*.

Equilibrate the column with a mixture of 43 volumes of mobile phase A and 57 volumes of mobile phase B.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-40	43→55	57→45	linear gradient
40-60	55→90	45→10	linear gradient
60-70	90	10	isocratic
70-75	90→43	10→57	linear gradient
75-85	43	57	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

www.webofpharma.com

https://thuocngocanh.com/

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.5;

in the chromatogram obtained with solution (4), the peak due to fluticasone propionate has a *signal-to-noise* ratio of at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the peak due to fluticasone propionate in the chromatogram obtained with solution (2) (0.5%),

the sum of the areas of any such peaks is not greater than 4 times the area of the peak due to fluticasone propionate in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the peak due to fluticasone propionate in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix the contents of 20 ampoules. Add 25 mL of *ethanol (65%)* to a quantity of the nasal drops containing 1 mg of Fluticasone Propionate, shake with the aid of ultrasound for 10 minutes. Add sufficient *ethanol (65%)* to produce 50 mL and filter.
(2) Dilute 2 mL of a 0.05% w/v solution of *fluticasone propionate BPCRS* in *methanol (80%)* to 50 mL with *ethanol (65%)*.
(3) 0.0004% w/v of *fluticasone impurity D EPCRS* and 0.002% w/v of *fluticasone propionate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile*, 35 volumes of 0.01M *ammonium dihydrogen orthophosphate* previously adjusted to pH 3.5 with *orthophosphoric acid* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.5. If necessary, adjust the proportion of *acetonitrile* in the mobile phase.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{25}H_{31}F_3O_5S$ in the nasal drops using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS*.

IMPURITIES

D. 6α,9-difluoro-17-[(methylsulfanyl)carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate (fluticasone *S*-methyl impurity; Ph. Eur. fluticasone impurity D).

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Nasal Spray

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluticasone Nasal Spray is a suspension of Fluticasone Propionate in a suitable liquid in a container fitted with an appropriate nasal delivery system.

The nasal spray complies with the requirements stated under Nasal Preparations and with the following requirements.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

80.0 to 120.0% of the amount stated to be delivered by actuation of the valve.

Carry out all the following procedures in the dark or under long-wavelength light (greater than 420 nm). Prepare solutions immediately before use and protect them from light.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the nasal spray containing 2 mg of Fluticasone Propionate add sufficient *acetonitrile* to produce 5 mL, shake for 3 minutes and filter.

(2) 0.04% w/v of *fluticasone propionate BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 40 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 8 volumes of *ethyl acetate* and 30 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the nasal spray containing 1 mg of Fluticasone Propionate to 10 mL with a mixture of equal volumes of mobile phase A and mobile phase B and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with a mixture of equal volumes of mobile phase A and mobile phase B.
(3) 0.02% w/v of *fluticasone propionate BPCRS* and 0.00004% w/v of *fluticasone impurity D EPCRS* in a mixture of equal volumes of mobile phase A and mobile phase B.
(4) Dilute 1 volume of solution (2) to 10 volumes with a mixture of equal volumes of mobile phase A and mobile phase B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use gradient elution and the mobile phases described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A A solution containing 0.05% v/v of *orthophosphoric acid* and 3.0% v/v of *methanol* *in* *acetonitrile*.

Mobile phase B A solution containing 0.05% v/v of *orthophosphoric acid* and 3.0% v/v of *methanol* *in* *water*.

Equilibrate the column with a mixture of 43 volumes of mobile phase A and 57 volumes of mobile phase B.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-40	43→55	57→45	linear gradient
40-60	55→90	45→10	linear gradient
60-70	90	10	isocratic
70-75	90→43	10→57	linear gradient
75-85	43	57	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

www.webofpharma.com

https://thuocngocanh.com/

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.5;

in the chromatogram obtained with solution (4), the peak due to fluticasone propionate has a *signal-to-noise* ratio of at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the peak due to fluticasone propionate in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any such peaks is not greater than 4 times the area of the peak due to fluticasone propionate in the chromatogram obtained with solution (2) (2%).

Disregard any peak with an area less than the area of the peak due to fluticasone propionate in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After priming the pump, discharge the container a sufficient number of times to obtain 1 mg of Fluticasone Propionate, add 25 mL of *ethanol (65%)* and shake with the aid of ultrasound for 10 minutes. Add sufficient *ethanol (65%)* to produce 50 mL, filter and use the filtrate.
(2) Dilute 2 mL of a 0.05% w/v solution of *fluticasone propionate BPCRS* in *methanol (80%)* to 50 mL with *ethanol (65%)*.
(3) 0.0004% w/v of *fluticasone impurity D EPCRS* and 0.002% w/v of *fluticasone propionate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile*, 35 volumes of 0.01M *ammonium dihydrogen orthophosphate* previously adjusted to pH 3.5 with *orthophosphoric acid* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.5. If necessary, adjust the proportion of *acetonitrile* in the mobile phase.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{25}H_{31}F_3O_5S$ in the nasal spray using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS*.

IMPURITIES

D. 6α,9-difluoro-17-[(methylsulfanyl)carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate (fluticasone *S*-methyl impurity; Ph. Eur. fluticasone impurity D).

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Ointment

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluticasone Ointment contains Fluticasone Propionate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Transfer a quantity of the ointment containing 0.1 mg of Fluticasone Propionate to a separating funnel, add 10 mL of *acetonitrile* and 50 mL of n-*hexane*, shake for 5 minutes and allow to separate. Filter the lower layer through an absorbent cotton plug previously washed with *acetonitrile*, extract the hexane layer with two 5 mL quantities of *acetonitrile*, filter each extract through the absorbent cotton plug and wash the absorbent cotton plug with 2 mL of *acetonitrile*. Add the washings to the combined filtrates, evaporate the resulting solution to dryness using a rotary evaporator at a temperature of 40° and dissolve the residue in 0.5 mL of *acetonitrile*.

(2) 0.020% w/v of *fluticasone propionate BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 12 cm.

(e) After removal of the plate, allow it to dry in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 8 volumes of *ethyl acetate* and 30 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) Transfer a quantity of the ointment containing 0.1 mg of Fluticasone Propionate to a separating funnel, add 45 mL of *n-hexane*, previously heated to 60° in a water bath, stopper the funnel and shake until the ointment is dispersed, venting frequently. Wash the stopper and neck of the funnel with 5 mL of *n-hexane* collecting the washings in the funnel, allow the funnel to cool to room temperature, add 10 mL of *methanol (80%)*, stopper, shake for 1 minute and allow to separate. Filter the lower aqueous layer through an absorbent cotton plug, previously washed with *methanol (80%)*, into a graduated flask; repeat the extraction with two 5-mL quantities of *methanol (80%)*, filtering the aqueous methanol extracts into the same graduated flask. Wash the absorbent cotton plug with 2 mL of *methanol (80%)*, collecting the washings in the flask and dilute the extract to 25 mL with *methanol (80%)*.

(2) 0.0004% w/v of *fluticasone propionate BPCRS* in *methanol (80%)*.

(3) 0.0004% w/v of *fluticasone impurity D EPCRS* and 0.002% w/v of *fluticasone propionate BPCRS* in *methanol (80%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 50°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile*, 35 volumes of 0.01M *ammonium dihydrogen orthophosphate* previously adjusted to pH 3.5 with *orthophosphoric acid* and 50 volumes of *methanol*.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fluticasone impurity D and fluticasone propionate is at least 1.6. If necessary, adjust the proportion of *acetonitrile* in the mobile phase.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{31}F_3O_5S$ in the ointment using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Pressurised Inhalation

General Notices

Action and use

Glucocorticoid.

DEFINITION

Fluticasone Pressurised Inhalation is a suspension of Fluticasone Propionate in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lung. The fine-particle characteristics of pressurised metered-dose preparations for inhalation are determined using the method described in Appendix XII C. 7. Preparations for Inhalation: Aerodynamic Assessment of Fine Particles.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$

80.0 to 120.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 300 nm of the final solution obtained in the test for Uniformity of delivered dose closely resembles that of a solution containing 0.0005% w/v of *fluticasone propionate BPCRS* in solvent A and exhibits a single maximum at 240 nm.

B. In the test for Uniformity of delivered dose, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the pressurised inhalation containing 0.5 mg of Fluticasone Propionate in 10 mL of a mixture of 7 volumes of *acetonitrile*, 20 volumes of *water* and 23 volumes of *methanol* and filter.

(2) Dilute 1 volume of solution (1) to 200 volumes in equal volumes of *acetonitrile* and *water*.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.02% w/v of *fluticasone propionate BPCRS* and 0.00004% w/v of *fluticasone* S-*methyl EPCRS* in equal volumes of *acetonitrile* and *water*.

(4) Dilute 1 volume of solution (2) to 5 volumes in equal volumes of *acetonitrile* and *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 23 volumes of *acetonitrile* and 77 volumes of *methanol*.

Mobile phase B 0.01M *ammonium dihydrogen orthophosphate*, adjusted to pH 3.5 with *acetic acid* or *dilute ammonia*.

Equilibrate the column with a mobile phase ratio A:B of 60:40. Inject solutions (1) and (3) and start the elution isocratically with the chosen mobile phase. One minute after elution of the apex of the fluticasone propionate peak start a linear gradient elution to reach a mobile phase ratio A:B of 85:15 over a period of 10 minutes. Continue the chromatography for 10 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to fluticasone propionate and fluticasone *S*-methyl impurity is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of delivered dose

Complies with the requirements stated under Pressurised Metered-dose Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 35 volumes of *water* add 65 volumes of *methanol* (solvent A).

(1) Collect single doses of the preparation being examined using the procedure described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose and dissolve the collected dose in sufficient of solvent A to produce a solution expected to contain 0.0005% w/v of Fluticasone Propionate.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.0005% w/v of *fluticasone propionate BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 239 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile*, 35 volumes of 0.01M *ammonium dihydrogen orthophosphate* and 50 volumes of *methanol* adjusted to pH 3.5 with *orthophosphoric acid* or *dilute ammonia*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the principal peak is not greater than 2.5.

DETERMINATION OF CONTENT

Calculate the content of Fluticasone Propionate, $C_{25}H_{31}F_3O_5S$, per delivered dose using the declared content of $C_{25}H_{31}F_3O_5S$ in *fluticasone propionate BPCRS*. Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of delivered dose.

© Crown Copyright 2022

www.webofpharma.com

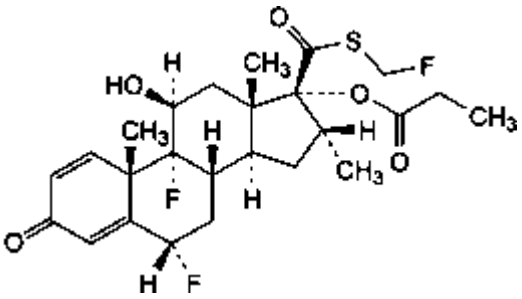
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluticasone Propionate

General Notices

(Ph. Eur. monograph 1750)



$C_{25}H_{31}F_3O_5S$ 500.6 *80474-14-2*

Action and use

Glucocorticoid.

Preparations

Fluticasone Cream

Fluticasone Inhalation Powder

Fluticasone Inhalation Powder, pre-metered

Fluticasone Nasal Drops

Fluticasone Nasal Spray

Fluticasone Ointment

Fluticasone Pressurised Inhalation

Fluticasone and Salmeterol Pressurised Inhalation Powder, pre-metered

Fluticasone and Salmeterol Pressurised Inhalation, suspension

Fluticasone and Salmeterol Inhalation Powder, Metered-Dose

Ph Eur

DEFINITION

www.webofpharma.com

https://thuocngocanh.com/

6α,9-Difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *fluticasone propionate CRS*.

TESTS

Specific optical rotation (*2.2.7*)

+ 32 to + 36 (anhydrous substance).

Dissolve 0.25 g in *methylene chloride R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Solvent mixture Mobile phase A, mobile phase B (50:50 *V/V*).

Test solution Dissolve 20 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 1 mg of *fluticasone impurity D CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 25 mL with the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *fluticasone propionate for system suitability CRS* (containing impurities G, J and K) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (d) Dissolve 2 mg of *fluticasone propionate for impurity C identification CRS* in the solvent mixture and dilute to 10 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: solution containing 0.05 per cent *V/V* of *phosphoric acid R* and 3.0 per cent *V/V* of *methanol R1* in *water for chromatography R*;

— *mobile phase B*: solution containing 0.05 per cent *V/V* of *phosphoric acid R* and 3.0 per cent *V/V* of *methanol R1* in *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	57	43
2 - 42	57 → 45	43 → 55
42 - 62	45 → 10	55 → 90
62 - 72	10	90

Flow rate 1 mL/min.

Detection Spectrophotometer at 239 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D; use the chromatogram supplied with *fluticasone propionate for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities G and J + K; use the chromatogram supplied with *fluticasone propionate for impurity C identification CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to fluticasone propionate (retention time = about 32 min): impurity C = about 0.8; impurity D = about 0.95; impurity G = about 1.30; impurities J and K = about 1.32.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity D and fluticasone propionate in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity J and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity G in the chromatogram obtained with

www.webofpharma.com

https://thuvienthuocngocanh.com/

reference solution (c).

Limits:

— *impurities D, G*: for each impurity, maximum 0.3 per cent;

— *impurity C*: maximum 0.2 per cent;

— *sum of impurities J and K*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.8 per cent;

— *reporting threshold*: 0.05 per cent (reference solution (b)).

Acetone

Gas chromatography (2.2.28).

Internal standard solution Dilute 0.5 mL of *tetrahydrofuran R* to 1000 mL with *dimethylformamide R*.

Test solution Dissolve 0.50 g of the substance to be examined in the internal standard solution and dilute to 10.0 mL with the internal standard solution.

Reference solution Dilute 0.40 g of *acetone R* to 100.0 mL with the internal standard solution. Dilute 1.0 mL of this solution to 10.0 mL with the internal standard solution.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.53 mm;

— *stationary phase*:*macrogol 20 000 R* (film thickness 2 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 5.5 mL/min.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 3.5	60
	3.5 - 7.5	60 → 180
	7.5 - 10.5	180

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Injection port		150
Detector		250

Detection Flame ionisation.

Injection 0.1 µL.

Limit:

— *acetone*: maximum 1.0 per cent *m/m*.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.100 g using the evaporation technique at 160 °C.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution Dissolve, using sonication, 20.0 mg of the substance to be examined in the mobile phase and dilute to 200.0 mL with the mobile phase. Dilute 4.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve, using sonication, 20.0 mg of *fluticasone propionate CRS* in the mobile phase and dilute to 200.0 mL with the mobile phase.

Reference solution (b) Dilute 4.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 1 mg of *fluticasone impurity D CRS* in the mobile phase and dilute to 25 mL with the mobile phase. To 1 mL of the solution add 2 mL of reference solution (a) and dilute to 5 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 15 volumes of *acetonitrile for chromatography R*, 35 volumes of a 1.15 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 3.5 and 50 volumes of *methanol R1*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 239 nm.

www.webofpharma.com

https://thuocngocanh.com/

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of fluticasone propionate.

Relative retention With reference to fluticasone propionate (retention time = about 6 min): impurity D = about 1.1.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to fluticasone propionate and impurity D; if necessary, adjust the ratio of acetonitrile to methanol in the mobile phase.

Calculate the percentage content of $C_{25}H_{31}F_3O_5S$ using the chromatogram obtained with reference solution (b) and taking into account the assigned content of *fluticasone propionate CRS*.

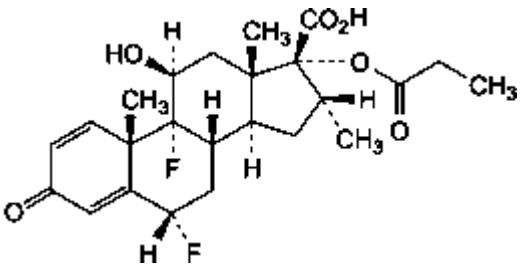
STORAGE

Protected from light.

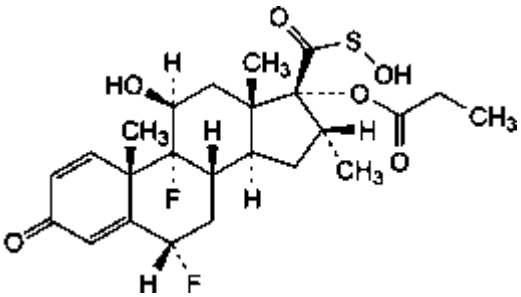
IMPURITIES

Specified impurities *C, D, G, J, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, E, F, H, I.*



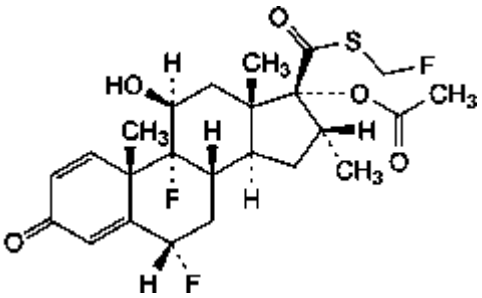
A. 6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo-17-(propanoyloxy)androsta-1,4-diene-17β-carboxylic acid,



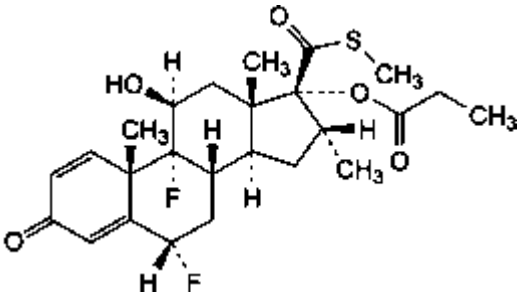
B. 6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo-17-(propanoyloxy)androsta-1,4-dien-17β-carbo(thioperoxoic) *SO*-acid,

www.webofpharma.com

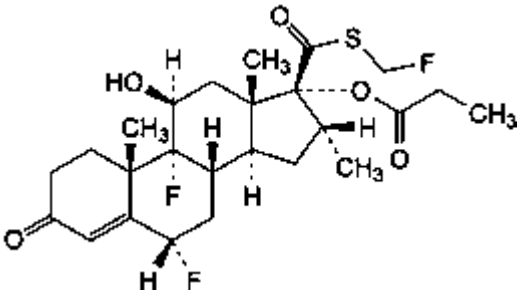
https://thuocngocanh.com/



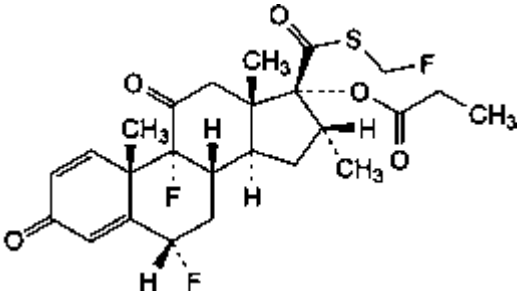
C. 6α,9-difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl acetate,



D. 6α,9-difluoro-11β-hydroxy-16α-methyl-17-[(methylsulfanyl)carbonyl]-3-oxoandrosta-1,4-dien-17α-yl propanoate,



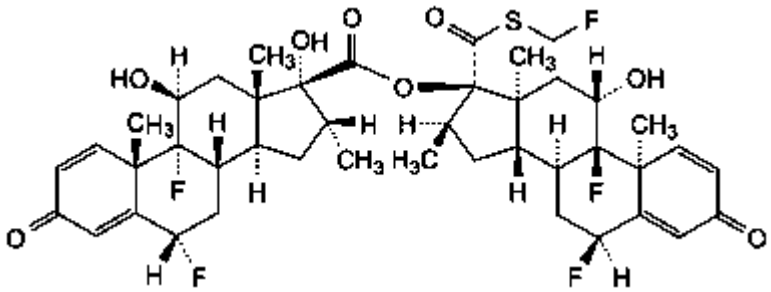
E. 6α,9-difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrost-4-en-17α-yl propanoate,



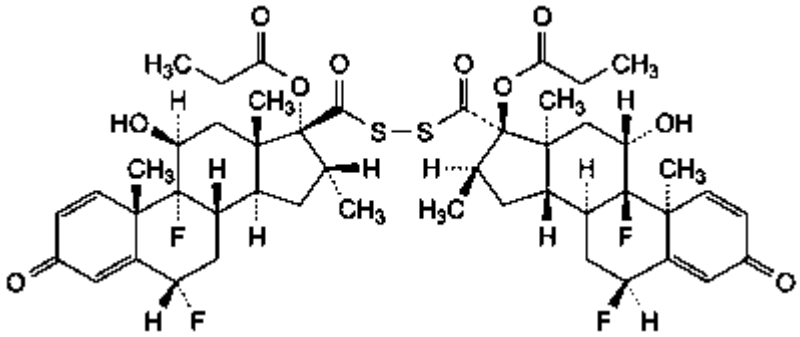
F. 6α,9-difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-16α-methyl-3,11-dioxoandrosta-1,4-dien-17α-yl propanoate,

www.webofpharma.com

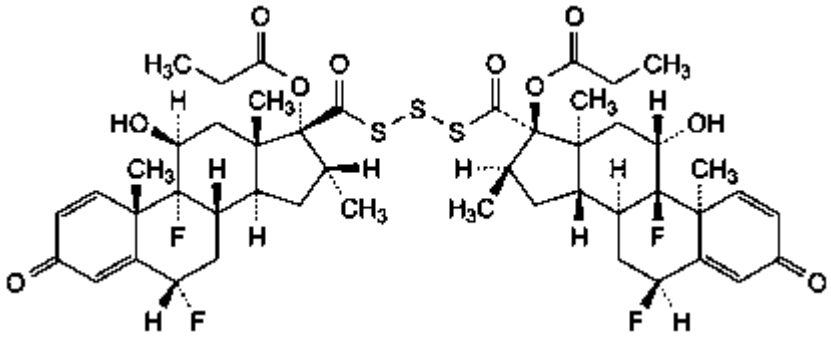
https://thuocngocanh.com/



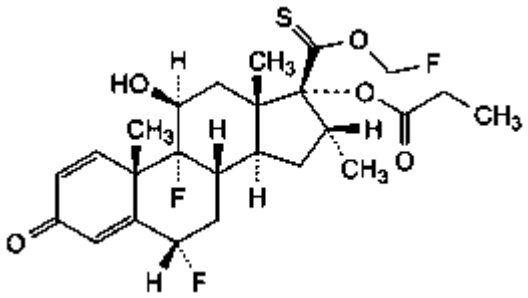
G. 6α,9-difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate,



H. 17,17′-(disulfanediyldicarbonyl)bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl) dipropanoate,



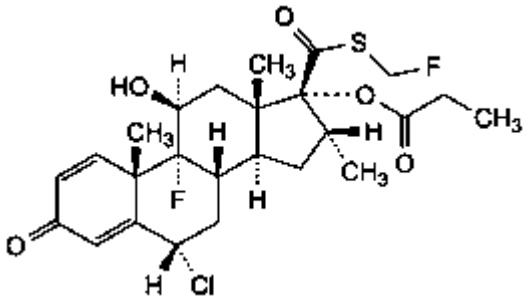
I. 17,17′-(trisulfanediyldicarbonyl)bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl) dipropanoate,



J. 6α,9-difluoro-17-[(fluoromethoxy)carbonothioyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate,

www.webofpharma.com

https://thuocngocanh.com/



K. 6α-chloro-9-fluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

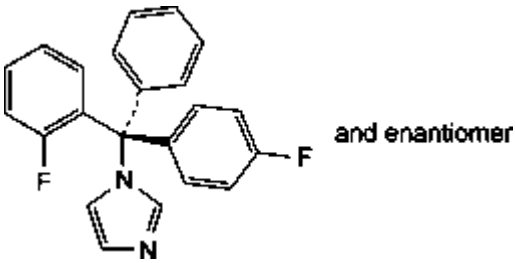
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Flutrimazole

General Notices

(Ph. Eur. monograph 1424)



$C_{22}H_{16}F_2N_2$ 346.4 *119006-77-8*

Action and use

Antifungal.

Ph Eur

DEFINITION

(*RS*)-1-[(2-Fluorophenyl)(4-fluorophenyl)phenylmethyl]-1*H*-imidazole.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in tetrahydrofuran, soluble in methanol.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 161 °C to 166 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation Discs.

Comparison *flutrimazole CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *flutrimazole CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *flutrimazole CRS* and 10 mg of *metronidazole benzoate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Pretreatment Heat the plate at 110 °C for 1 h.

Mobile phase *2-propanol R*, *ethyl acetate R* (10:90 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter. Add 1.0 mL of the filtrate to a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow and the blank is red.

TESTS

Solution S

Dissolve 1.00 g in *methanol R* and dilute to 50.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is not more opalescent than reference suspension II (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Optical rotation (2.2.7)

-0.05° to + 0.05°, determined on solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *imidazole CRS* (impurity A) in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 30.0 mg of *flutrimazole impurity B CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (c) Mix 2.0 mL of reference solution (a) and 2.0 mL of reference solution (b) and dilute to 50.0 mL with the mobile phase.

Reference solution (d) Dilute 10.0 mL of reference solution (c) to 50.0 mL with the mobile phase.

Reference solution (e) Mix 2.0 mL of the test solution and 10.0 mL of reference solution (c) and dilute to 50.0 mL with the mobile phase.

Reference solution (f) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.2 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 0.03 M phosphate buffer solution pH 7.0 R, *acetonitrile R* (40:60 *V/V*).

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 2.5 times the retention time of flutrimazole.

System suitability Reference solution (e):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 2.0 between the peaks due to impurity A (1st peak) and impurity B (2nd peak); minimum 1.5 between the peaks due to impurity B and flutrimazole (3rd peak);

— *symmetry factors*: maximum 2.0 for the peaks due to impurities A and B.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.1 per cent);

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (f) (0.10 per cent);

— *sum of impurities other than B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (f) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (f) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 34.64 mg of $C_{22}H_{16}F_2N_2$.

STORAGE

Protected from light.

IMPURITIES

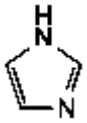
Specified impurities A, B.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

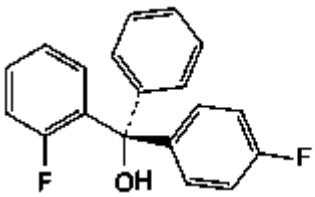
www.webofpharma.com

https://thuocngocanh.com/

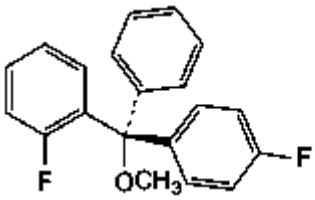
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.



A. imidazole,



B. (*RS*)-(2-fluorophenyl)(4-fluorophenyl)phenylmethanol,



C. (*RS*)-(2-fluorophenyl)(4-fluorophenyl)methoxyphenylmethane.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluvastatin Capsules

General Notices

Action and use

HMG Co-A reductase inhibitor; lipid regulating drug.

DEFINITION

Fluvastatin Capsules contain Fluvastatin Sodium.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of fluvastatin, $C_{24}H_{26}FNO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Mix with the aid of ultrasound a quantity of capsule contents containing the equivalent of 20 mg of fluvastatin with 25 mL of *methanol*. Dilute to 100 mL with *methanol*, filter through a 0.45-µm nylon filter and use the filtrate.

(2) 0.021% w/v of *fluvastatin sodium BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (366 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 9 volumes of *toluene*, 15 volumes of *methanol* and 25 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, and rotate the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with sufficient dissolution medium, if necessary, to produce a solution expected to contain the equivalent of 0.0022% w/v of fluvastatin.

(2) 0.0023% w/v of *fluvastatin sodium BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC Pack Pro S C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 305 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

200 volumes of *acetonitrile*, 300 volumes of *methanol* and 500 volumes of 0.069M *tetramethylammonium hydroxid*e, previously adjusted to pH 7.2 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of fluvastatin, $C_{24}H_{26}FNO_4$, in the medium from the chromatograms obtained and using the declared content of $C_{24}H_{25}FNNaO_4$ in *fluvastatin sodium BPCRS*. Each mg of $C_{24}H_{25}FNNaO_4$ is equivalent to 0.950 mg of $C_{24}H_{26}FNO_4$.

LIMITS

The amount of fluvastatin released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the contents of the capsules containing the equivalent of 25 mg of fluvastatin in 20 mL of mobile phase B. Add sufficient mobile phase A to produce a solution containing the equivalent of 0.05% w/v of fluvastatin and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

(3) Dilute 1 volume of solution (2) to 5 volumes with mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

(4) Dissolve the contents of a vial of *fluvastatin for system suitability EPCRS* in 1 mL of a mixture of equal volumes of mobile phase A and mobile phase B.

(5) 0.0005% w/v of *fluvastatin impurity F BPCRS* a mixture of equal volumes of mobile phase A and mobile phase B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC Pack pro C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use detection wavelengths of 305 nm and 365 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Add 20 volumes of 1.38M *tetramethylammonium hydroxide* to 880 volumes of *water* and adjust to pH 7.2 with *orthophosphoric acid*; mix with 40 volumes of *acetonitrile* and 60 volumes of *methanol*.

Mobile phase B Add 20 volumes of 1.38M *tetramethylammonium hydroxide* to 80 volumes of *water* and adjust to pH 7.2 with *orthophosphoric acid*; mix with 360 volumes of *acetonitrile* and 540 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	70	30	isocratic
3-23	70→10	30→90	linear gradient
23-28	10	90	isocratic
28-30	10→70	90→30	linear gradient
30-35	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to fluvastatin (retention time about 14 minutes) are: impurity A, about 1.05; impurity D, about 1.1; impurity F, about 1.2; and impurity B, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) at 305 nm, the *peak-to-valley ratio* is at least 5 where H_p is the height above the baseline of the peak due to impurity A and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to fluvastatin.

LIMITS

Use the chromatogram supplied with *fluvastatin for system suitability EPCRS* and the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B and D.

www.webofpharma.com

https://thuocngocanh.com/

Use the chromatogram supplied with *fluvastatin impurity F BPCRS* and the chromatogram obtained with solution (5) to identify the peak due to impurity F in the chromatogram obtained with solution (1).

At a detection wavelength of 305 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (1.0%);

the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

Disregard any peak with an area less than half the area of the principal peak nm in the chromatogram obtained with solution (3) (0.1%).

At a detection wavelength of 365 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D at 365 nm is not greater than half the area of the principal peak at 305 nm in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve a quantity of the mixed contents of 20 capsules containing the equivalent of 25 mg of fluvastatin in 50 mL of mobile phase. Dilute 1 volume to 10 volumes with the mobile phase (to produce a solution containing the equivalent of 0.005% w/v of fluvastatin) and filter.

(2) 0.0053% w/v of *fluvastatin sodium BPCRS* in the mobile phase.

(3) Dissolve the contents of a vial of *fluvastatin for system suitability EPCRS* in 1 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fluvastatin and impurity A is at least 1.5.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuvienthuocngocanh.com/

Calculate the content of $C_{24}H_{26}FNO_4$, in the capsules using the declared content of $C_{24}H_{25}FNNaO_4$ in *fluvastatin sodium BPCRS*. Each mg of $C_{24}H_{25}FNNaO_4$ is equivalent to 0.950 mg of $C_{24}H_{26}FNO_4$.

STORAGE

Fluvastatin Capsules should be protected from light.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of fluvastatin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Fluvastatin Sodium.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluvastatin Prolonged-release Tablets

General Notices

Proonged-release Fluvastatin Tablets

Action and use

HMG Co-A reductase inhibitor; lipid regulating drug.

DEFINITION

Fluvastatin Prolonged-release Tablets contain Fluvastatin Sodium. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of fluvastatin. The dissolution profile reflects the *in-vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of fluvastatin, $C_{24}H_{26}FNO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 100 mg of fluvastatin with 10 mL of *methanol* and filter through a 0.45-µm PTFE filter. Evaporate the filtrate to dryness and dry the residue at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of *fluvastatin sodium* (*RS 479*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 25 mg of fluvastatin with 20 mL of mobile phase B. Add sufficient mobile phase A to produce a solution containing the equivalent of 0.05% w/v of fluvastatin and filter through a 0.45-µm PTFE filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

(3) Dilute 1 volume of solution (2) to 5 volumes with mobile phase A.

(4) Dissolve the contents of a vial of *fluvastatin for system suitability EPCRS* in 1 mL of a mixture of equal volumes of mobile phase A and mobile phase B.

(5) 0.00025% w/v of *fluvastatin impurity F BPCRS* in a mixture of equal volumes of mobile phase A and mobile phase B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC Pack Pro S C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use detection wavelengths of 305 nm and 365 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Add 20 volumes of 1.38M *tetramethylammonium hydroxide* to 880 volumes of *water* and adjust quickly to pH 7.2 with *orthophosphoric acid*; mix with 40 volumes of *acetonitrile* and 60 volumes of *methanol*.

Mobile phase B Add 20 volumes of 1.38M *tetramethylammonium hydroxide* to 80 volumes of *water* and adjust quickly to pH 7.2 with *orthophosphoric acid*; mix with 360 volumes of *acetonitrile* and 540 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	70	30	isocratic
3-23	70→10	30→90	linear gradient
23-28	10	90	isocratic
28-30	10→70	90→30	linear gradient
30-35	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to fluvastatin (retention time about 14 minutes) are: impurity A, about 1.05; impurity D, about 1.1, impurity F, about 1.2 and impurity B, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4) at 305 nm, the *peak-to-valley ratio* is at least 5 where H_p is the height above the baseline of the peak due to impurity A and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to fluvastatin.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

Use the chromatogram supplied with *fluvastatin for system suitability EPCRS* and the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B and D.

Use the chromatogram supplied with *fluvastatin impurity F BPCRS* and the chromatogram obtained with solution (5) to identify the peak due to impurity F in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A at 305 nm is not greater than the area of the principal peak at 305 nm in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity D at 365 nm is not greater than half the area of the principal peak at 305 nm in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity F at 305 nm is not greater than the area of the principal peaks at 305 nm in the chromatogram obtained with solution (5) (0.5%);

the area of any other *secondary peak* at 305 nm is not greater than the area of the principal peak at 305 nm in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks* at 305 nm is not greater than twice the area of the principal peak at 305 nm in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak at 305 nm with an area less than half the area of the principal peak at 305 nm in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Mix with the aid of ultrasound, a quantity of the powdered tablets containing the equivalent of 25 mg of fluvastatin in 50 mL of the mobile phase. Dilute 1 volume to 10 volumes and filter.
(2) 0.0053% w/v of *fluvastatin sodium BPCRS*.
(3) Dissolve the contents of a vial of *fluvastatin for system suitability EPCRS* in 1 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC Pack Pro S C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 305 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuathuocngocanh.com/

200 volumes of *acetonitrile*, 300 volumes of *methanol* and 500 volumes of 0.069M *tetramethylammonium hydroxide*, which was previously quickly adjusted to pH 7.2 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fluvastatin and impurity A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{26}FNO_4$, in the tablets using the declared content of $C_{24}H_{25}FNNaO_4$ in *fluvastatin sodium BPCRS*. Each mg of $C_{24}H_{25}FNNaO_4$ is equivalent to 0.9493 mg of $C_{24}H_{26}FNO_4$.

STORAGE

Fluvastatin Prolonged-release Tablets should be protected from light and moisture.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of fluvastatin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Fluvastatin Sodium.

© Crown Copyright 2022

www.webofpharma.com

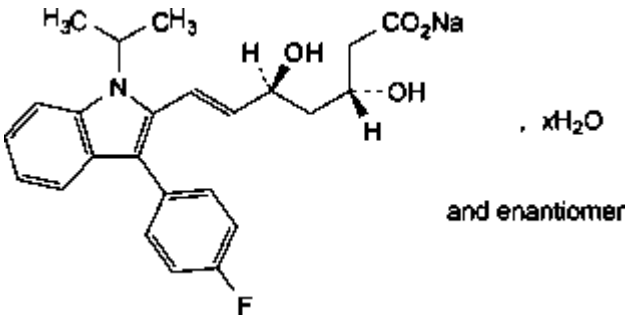
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluvastatin Sodium

General Notices

(Ph. Eur. monograph 2333)



$C_{24}H_{25}FNNaO_4,xH_2O$ 433.5 (anhydrous substance)

Anhydrous fluvastatin sodium *93957-55-2*

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

Preparations

Fluvastatin Capsules

Fluvastatin Prolonged-release Tablets

Ph Eur

DEFINITION

Sodium (3*RS*,5*SR*,6*E*)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxyhept-6-enoate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

It may be anhydrous or contain a variable quantity of water.

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, or pale yellow or pale reddish-yellow, very hygroscopic, amorphous or crystalline powder.

Solubility

Soluble in water, freely soluble in methanol, practically insoluble in acetonitrile.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *fluvastatin sodium CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness on a steam bath, protecting the solutions from light, and dry at 105 °C for 30 min. Cool and keep in a desiccator. Record new spectra using the residues.

B. 0.5 mL of solution S (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

pH (*2.2.3*)

8.0 to 10.0 for solution S.

Related substances

Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution Dissolve 25 mg of the substance to be examined in 20 mL of mobile phase B and dilute to 50.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 50.0 mL with mobile phase A.

Reference solution (b) Dissolve the contents of a vial of *fluvastatin for system suitability CRS* (containing impurities A, B and D) in 1.0 mL of a mixture of equal volumes of mobile phase A and mobile phase B.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: to 880 mL of *water R* add 20 mL of a 250 g/L solution of *tetramethylammonium hydroxide R* and adjust quickly to pH 7.2 with *phosphoric acid R*; mix with 100 mL of a mixture of 40 volumes of *acetonitrile R* and 60 volumes of *methanol R*;

— *mobile phase B*: to 80 mL of *water R* add 20 mL of a 250 g/L solution of *tetramethylammonium hydroxide R* and adjust quickly to pH 7.2 with *phosphoric acid R*; mix with 900 mL of a mixture of 40 volumes of *acetonitrile R* and 60 volumes of *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	70	30
3 - 23	70 → 10	30 → 90
23 - 28	10	90

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 305 nm and at 365 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *fluvastatin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and D.

Relative retention With reference to fluvastatin (retention time = about 14 min): impurity A = about 1.05; impurity D = about 1.1; impurity B = about 1.6.

System suitability Reference solution (b) at 305 nm:

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to fluvastatin.

Limits:

— *impurity A at 305 nm*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);

— *impurity B at 305 nm*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity D at 365 nm*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (a) at 305 nm (0.15 per cent);

— *unspecified impurities at 305 nm*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *sum of impurities at 305 nm*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit at 305 nm*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 12.0 per cent, determined on 0.200 g.

ASSAY

Dissolve 0.325 g in 50 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 43.35 mg of $C_{24}H_{25}FNNaO_4$.

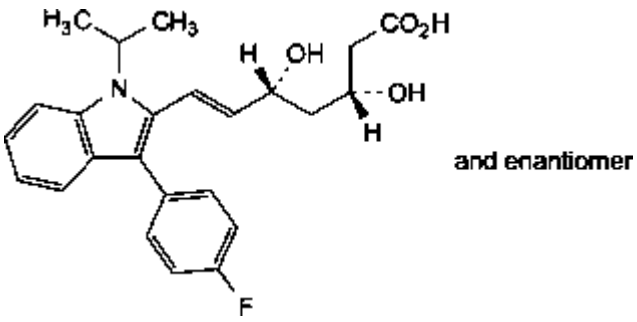
STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities *A, B, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, F, G.*

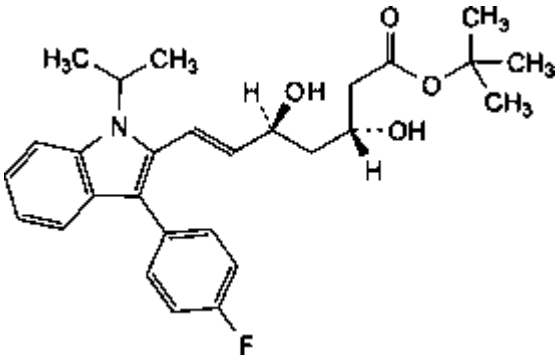


and enantiomer

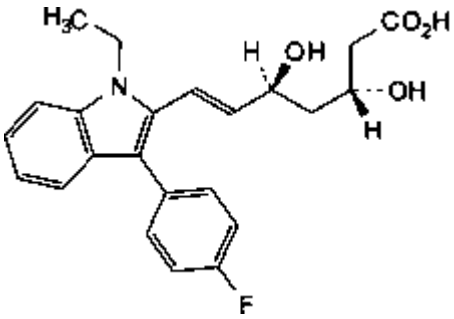
A. (3*RS*,5*RS*,6*E*)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxyhept-6-enoic acid,

www.webofpharma.com

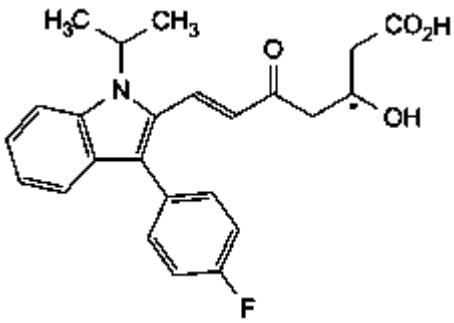
https://thuocngocanh.com/



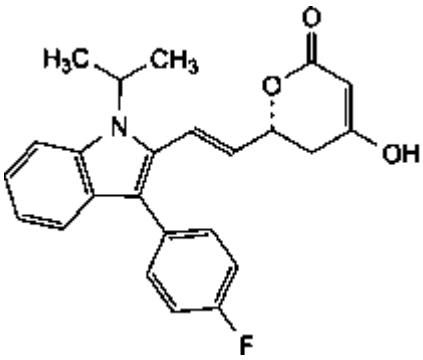
B. 1,1-dimethylethyl (3*R*,5*S*,6*E*)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxyhept-6-enoate,



C. (3*R*,5*S*,6*E*)-7-[1-ethyl-3-(4-fluorophenyl)-1*H*-indol-2-yl]-3,5-dihydroxyhept-6-enoic acid,



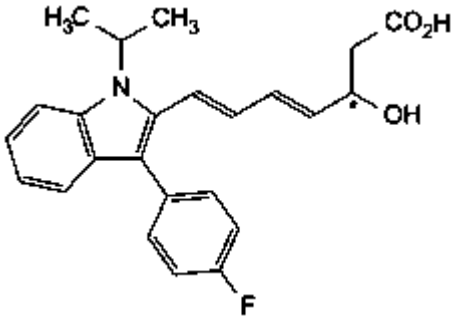
D. (6*E*)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3-hydroxy-5-oxohept-6-enoic acid,



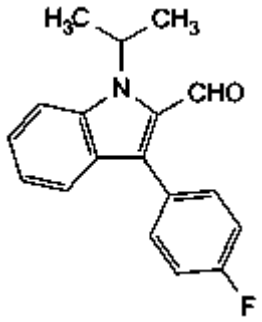
E. (6*R*)-6-[(*E*)-2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]ethenyl]-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one,

www.webofpharma.com

https://thuocngocanh.com/



F. (4*E*,6*E*)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3-hydroxyhepta-4,6-dienoic acid,



G. 3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indole-2-carbaldehyde.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

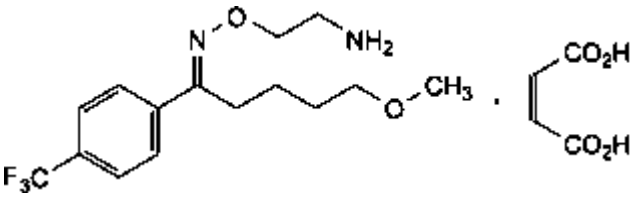
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluvoxamine Maleate

General Notices

(Ph. Eur. monograph 1977)



$C_{19}H_{25}F_3N_2O_6$ 434.4 *61718-82-9*

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

Preparation

Fluvoxamine Tablets

Ph Eur

DEFINITION

2-[[[(1*E*)-5-Methoxy-1-[4-(trifluoromethyl)phenyl]pentylidene]amino]oxy]ethanamine (*Z*)-butenedioate.

Content

99.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

The production method must be evaluated to determine the potential for formation of aziridine. Where necessary, a validated test for the substance is carried out or the production method is validated to demonstrate acceptable clearance.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Sparingly soluble in water, freely soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *fluvoxamine maleate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the test solution immediately before use.*

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 25 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *fluvoxamine for system suitability CRS* (containing impurities A, B, C and F) in 1.0 mL of the mobile phase.

Reference solution (c) Dissolve 3.0 mg of *fluvoxamine impurity D CRS* in 5 mL of the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 370 volumes of *acetonitrile R1* and 630 volumes of a buffer solution containing 1.1 g/L of *potassium dihydrogen phosphate R* and 1.9 g/L of *sodium pentanesulfonate R* in *water R*, previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 234 nm.

Injection 20 µL.

Run time 6 times the retention time of fluvoxamine.

Identification of impurities Use the chromatogram supplied with *fluvoxamine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and F.

Relative retention With reference to fluvoxamine (retention time = about 15 min): maleic acid = about 0.15; impurities F and G = about 0.5; impurity C = about 0.6; impurity B = about 0.8; impurity A = about 2.5; impurity D = about 5.4.

System suitability Reference solution (b):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 1.5 between the peaks due to impurities F and C.

Limits:

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *sum of impurities F and G*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to maleic acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 80 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 43.44 mg of $C_{19}H_{25}F_3N_2O_6$.

IMPURITIES

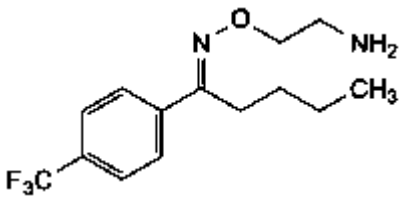
Specified impurities *A, B, C, D, F, G.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

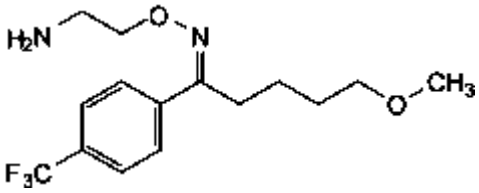
www.webofpharma.com

https://thuocngocanh.com/

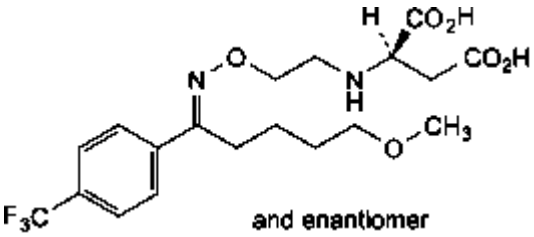
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) E, I, J.



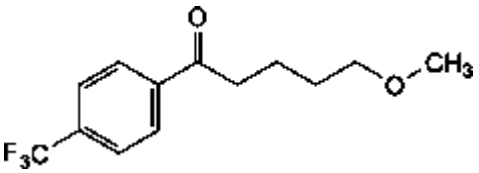
A. 2-[[[(1*E*)-1-[4-(trifluoromethyl)phenyl]pentylidene]amino]oxy]ethanamine,



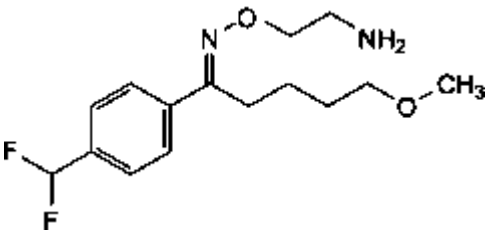
B. 2-[[[(1*Z*)-5-methoxy-1-[4-(trifluoromethyl)phenyl]pentylidene]amino]oxy]ethanamine,



C. (2*RS*)-2-[[2-[[[(1*E*)-5-methoxy-1-[4-(trifluoromethyl)phenyl]pentylidene]amino]oxy]ethyl]amino]butanedioic acid,



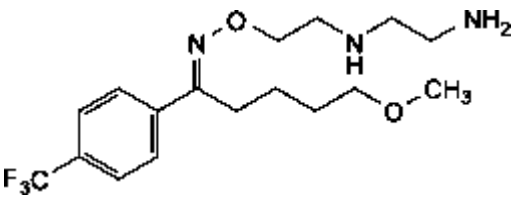
D. 5-methoxy-1-[4-(trifluoromethyl)phenyl]pentan-1-one,



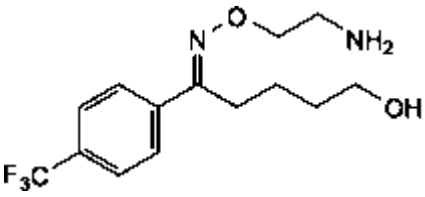
E. 2-[[[(1*E*)-1-[4-(difluoromethyl)phenyl]-5-methoxypentylidene]amino]oxy]ethanamine,

www.webofpharma.com

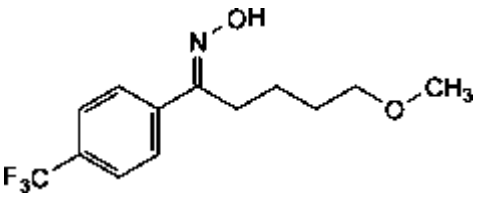
https://thuocngocanh.com/



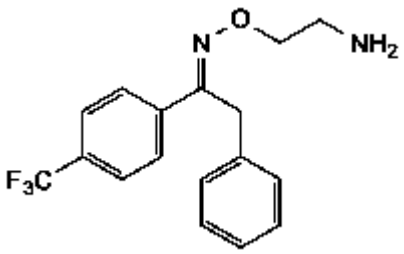
F. *N*-[2-[[[(1*E*)-5-methoxy-1-[4-(trifluoromethyl)phenyl]pentylidene]amino]oxy]ethyl]ethane-1,2-diamine,



G. (5*E*)-5-[(2-aminoethoxy)imino]-5-[4-(trifluoromethyl)phenyl]pentan-1-ol,



I. (*E*)-*N*-[5-methoxy-1-[4-(trifluoromethyl)phenyl]pentylidene]hydroxylamine,



J. 2-[[[(1*E*)-2-phenyl-1-[4-(trifluoromethyl)phenyl]ethylidene]amino]oxy]ethanamine.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fluvoxamine Tablets

General Notices

Action and use

Selective serotonin reuptake inhibitor; antidepressant.

DEFINITION

Fluvoxamine Tablets contain Fluvoxamine Maleate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of fluvoxamine maleate, $C_{15}H_{21}F_3N_2O_2,C_4H_4O_4$

92.5 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Fluvoxamine Maleate with 10 mL of *acetonitrile* for 10 minutes, centrifuge and evaporate the supernatant liquid to dryness using a rotary evaporator. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of fluvoxamine maleate *(RS 159)*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

After 20 minutes withdraw a 10-mL sample of the medium and centrifuge. Measure the *absorbance* of the clear supernatant liquid, suitably diluted with *water* if necessary, at the maximum at 244 nm, Appendix II B using *water* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of fluvoxamine maleate, $C_{15}H_{21}F_3N_2O_2,C_4H_4O_4$, in the medium taking 270 as the value of A(1%, 1 cm) at the maximum at 244 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.25 g of Fluvoxamine Maleate with 125 mL of the mobile phase for 10 minutes, add sufficient mobile phase to produce 250 mL, mix, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Heat a 0.32% w/v solution of *fluvoxamine maleate impurity standard BPCRS* in 0.1M *hydrochloric acid* on a water bath for 10 minutes (generation of impurity C).

(4) 0.0008% w/v of *fluvoxamine impurity D BPCRS* in the mobile phase.

(5) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.0 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 5 µL of each solution.

(g) Allow the chromatography to proceed for 2.5 times the retention time of fluvoxamine.

MOBILE PHASE

40 volumes of a solution containing 1.25% w/v of *diammonium hydrogen orthophosphate* and 0.275% w/v of *sodium heptanesulfonate monohydrate* and 60 volumes of *methanol*, adjusting the pH of the mixture to 3.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to fluvoxamine (retention time about 8 minutes) are: maleic acid, about 0.2; impurity C, about 0.6; impurity F, about 0.7; impurity B, about 0.8; impurity D, about 1.6 and impurity A, about 2.0.

SYSTEM SUITABILITY

The test is not valid unless, the chromatogram obtained with solution (3):

closely resembles the reference chromatogram supplied with *fluvoxamine maleate impurity standard BPCRS;*

the *resolution* between the peaks corresponding to fluvoxamine and impurity B is at least 1.5.

LIMITS

Identify the impurities from the chromatogram obtained with solution (3) and the chromatogram supplied with the *fluvoaxmine maleate impurity standard BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity B is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.8%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all of the secondary peaks, other than any peaks corresponding to impurity C and impurity D, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard the peak corresponding to maleic acid and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.25 g of Fluvoxamine Maleate with 125 mL of the mobile phase for 10 minutes, add sufficient of the mobile phase to produce 250 mL, mix, centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with the mobile phase.
(2) 0.010% w/v of *fluvoxamine maleate BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{21}F_3N_2O_2,C_4H_4O_4$ in the tablets using the declared content of $C_{15}H_{21}F_3N_2O_2,C_4H_4O_4$ in *fluvoxamine maleate BPCRS*.

STORAGE

Fluvoxamine Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, C, D, and F listed under Fluvoxamine Maleate.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

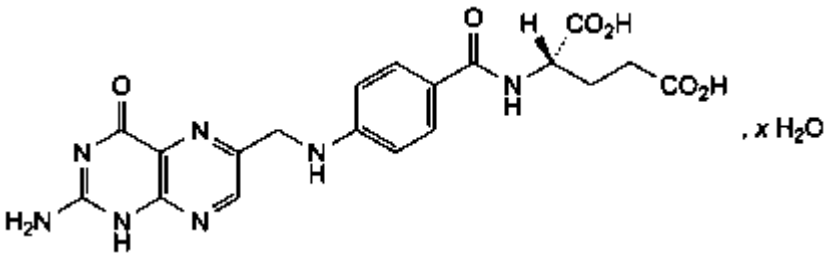
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Folic Acid Hydrate

General Notices

Folic Acid

(Ph. Eur. monograph 0067)



$C_{19}H_{19}N_7O_6,xH_2O$ 441.4 (anhydrous substance)

Anhydrous folic acid *59-30-3*

Action and use

Vitamin B component.

Preparations

Folic Acid Injection

Folic Acid Oral Solution

Folic Acid Tablets

Ferrous Fumarate and Folic Acid Tablets

Ph Eur

DEFINITION

(2*S*)-2-[4-[[(2-Amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino]benzamido]pentanedioic acid hydrate.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

CHARACTERS

Appearance

Yellowish or orange, crystalline powder.

Solubility

Practically insoluble in water and in most organic solvents. It dissolves in dilute acids and in alkaline solutions.

IDENTIFICATION

First identification: A, B, D.

Second identification: A, C.

A. Specific optical rotation (2.2.7): + 18 to + 22 (anhydrous substance).
Dissolve 0.25 g in a 4.2 g/L solution of *sodium hydroxide R* and dilute to 25.0 mL with the same solution.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *folic acid CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in a mixture of 2 volumes of *concentrated ammonia R* and 9 volumes of *methanol R*, and dilute to 100 mL with the same mixture of solvents.

Reference solution Dissolve 50 mg of *folic acid CRS* in a mixture of 2 volumes of *concentrated ammonia R* and 9 volumes of *methanol R*, and dilute to 100 mL with the same mixture of solvents.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *propanol R*, *ethanol (96 per cent) R* (20:20:60 *V/V/V*).

Application 2 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 365 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, fluorescence and size to the principal spot in the chromatogram obtained with the reference solution.

D. Water (see Tests).

TESTS

www.webofpharma.com

https://thuvienthuocngocanh.com/

Related substances

Liquid chromatography (2.2.29).

Solution A 28.6 g/L solution of *sodium carbonate R*.

Test solution Dissolve 50.0 mg of the substance to be examined in 2.5 mL of solution A and dilute to 50.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *folic acid CRS* in 2.5 mL of solution A and dilute to 50.0 mL with the mobile phase. Dilute 2.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *folic acid for system suitability CRS* (containing impurities C, E, G and H) in 1 mL of solution A and dilute to 25 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (d) Dissolve 10.0 mg of *folic acid impurity A CRS* in 1 mL of solution A and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (e) Dissolve 4.0 mg of *folic acid impurity D CRS* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (f) Dissolve 5 mg of *folic acid for impurity I identification CRS* in 1 mL of solution A and dilute to 25 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: spherical *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 12 volumes of *methanol R* and 88 volumes of a solution containing 11.16 g/L of *potassium dihydrogen phosphate R* and 5.50 g/L of *dipotassium hydrogen phosphate R*; adjust to pH 6.4 with *dilute phosphoric acid R*.

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 5 µL of the test solution and reference solutions (b), (c), (d), (e) and (f).

Run time 3.3 times the retention time of folic acid.

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity A; use the chromatogram supplied with *folic acid for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C, E, G and H; use the chromatogram obtained with reference solution (e) to identify the peak due to impurity D;

www.webofpharma.com

https://thuocngocanh.com/

use the chromatogram supplied with *folic acid for impurity I identification CRS* and the chromatogram obtained with reference solution (f) to identify the peak due to impurity I.

Relative retention With reference to folic acid (retention time = about 8.5 min): impurity A = about 0.5; impurity C = about 0.9; impurity E = about 1.3; impurity D = about 1.5; impurity I = about 2.15; impurity G = about 2.4; impurity H = about 2.5.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to folic acid and impurity E;

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to folic acid; minimum 1.5, where H_p = height above the baseline of the peak due to impurity G and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity H.

Calculation of percentage contents:

— for impurity A, use the concentration of impurity A in reference solution (d);

— for impurity D, use the concentration of impurity D in reference solution (e);

— for impurities other than A and D, use the concentration of folic acid hydrate in reference solution (c).

Limits:

— *impurity A*: maximum 0.5 per cent;

— *impurity D*: maximum 0.4 per cent;

— *impurities C, E, G*: for each impurity, maximum 0.3 per cent;

— *impurities H, I*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.2 per cent;

— *reporting threshold*: 0.05 per cent.

Water (2.5.12)

5.0 per cent to 8.5 per cent, determined on 0.150 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

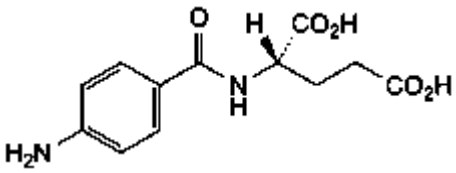
STORAGE

Protected from light, under inert gas.

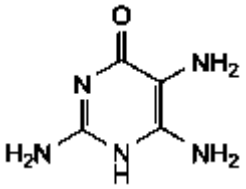
IMPURITIES

Specified impurities *A, C, D, E, G, H, I.*

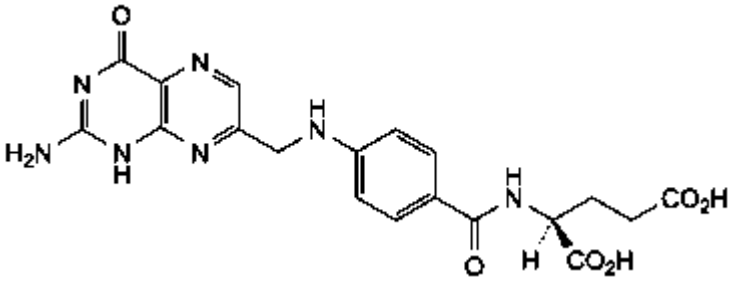
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, F.*



A. (2*S*)-2-(4-aminobenzamido)pentanedioic acid (*N*-(4-aminobenzoyl)-L-glutamic acid),



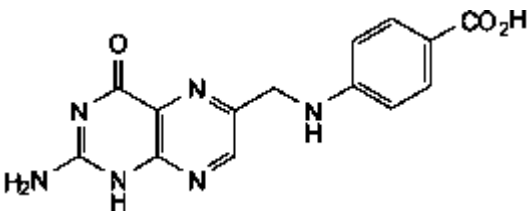
B. 2,5,6-triaminopyrimidin-4(1*H*)-one,



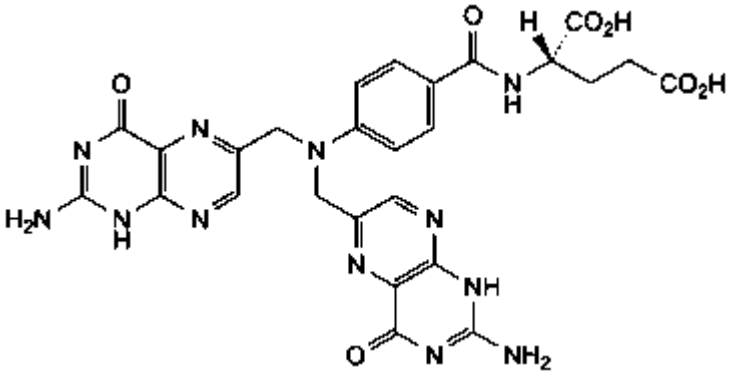
C. (2*S*)-2-[4-[[(2-amino-4-oxo-1,4-dihydropteridin-7-yl)methyl]amino]benzamido]pentanedioic acid (isofolic acid),

www.webofpharma.com

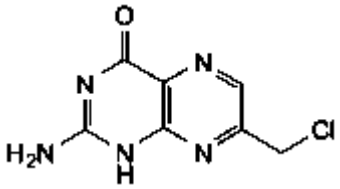
https://thuocngocanh.com/



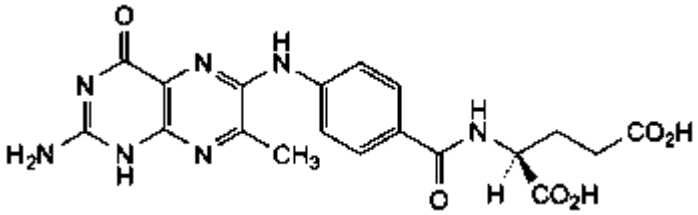
D. 4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino]benzoic acid (pteroic acid),



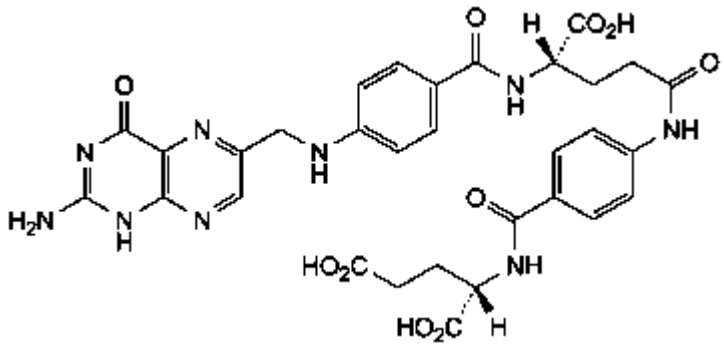
E. (2*S*)-2-[4-[bis[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino]benzamido]pentanedioic acid (6-pterinylfolic acid),



F. 2-amino-7-(chloromethyl)pteridin-4(1*H*)-one,



G. (2*S*)-[4-[(2-amino-7-methyl-4-oxo-1,4-dihydropteridin-6-yl)amino]benzamido]pentanedioic acid,



www.webofpharma.com

https://thuocngocanh.com/

H. (2*S*)-2-[4-[(4*S*)-4-[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino]benzamido]-4-carboxybutanamido]benzamido]pentanedioic acid,

I. unknown structure.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Folic Acid Injection

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Vitamin B component.

DEFINITION

Folic Acid Injection is a sterile solution of Folic Acid Hydrate in a suitable liquid.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements. Where appropriate, the injection also complies with the requirements stated under Unlicensed Medicines.

Content of folic acid, $C_{19}H_{19}N_7O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the injection containing the equivalent of 15 mg of folic acid with sufficient of a mixture of 1 volume of 13.5M *ammonia* and 9 volumes of *methanol* to produce 30 mL.

(2) 0.05% w/v of *folic acid BPCRS* in a mixture of 2 volumes of 13.5M *ammonia* and 9 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

20 volumes of 13.5M *ammonia*, 20 volumes of *propan-1-ol* and 60 volumes of *ethanol (96%)*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, fluorescence and size to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 7.0 to 9.0, Appendix V L.

Hydrolysis products

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Dilute a quantity of the injection with sufficient of the mobile phase to produce a solution containing the equivalent of 0.01% w/v of folic acid.

(2) 0.00005% w/v of *4-aminobenzoic acid* and 0.0002% w/v of *N*-(4-aminobenzoyl)-L-glutamic acid in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 269 nm.

(f) Inject 20 µL of each solution.

In the chromatogram obtained with solution (2) the substances elute in the following order: *N*-(4-aminobenzoyl)-L-glutamic acid; 4-aminobenzoic acid.

MOBILE PHASE

0.05M *potassium dihydrogen orthophosphate*, adjusted to pH 5.5 with 5M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminobenzoic acid is not greater than the area of the peak due to 4-aminobenzoic acid in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to *N*-(4-aminobenzoyl)-L-glutamic acid is not greater than the area of the peak due to *N*-(4-aminobenzoyl)-L-glutamic acid in the chromatogram obtained with solution (2) (2%).

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a quantity of the injection containing the equivalent of 7.5 mg of folic acid to 100 mL with a buffer solution prepared by diluting 25 volumes of 0.1M *anhydrous sodium dihydrogen orthophosphate*, adjusted to pH 4.0 with 0.1M *sodium hydroxide*, to 250 volumes with *water*.

(2) 0.0075% w/v of *folic acid BPCRS* in the buffer solution.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Lichrosorb RP-18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

4 volumes of *acetonitrile*, 6 volumes of *methanol* and 90 volumes of 0.01M *sodium acetate*, adjusted to pH 4.5 with *acetic acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in the injection using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Folic Acid Oral Solution

General Notices

Action and use

Vitamin B component.

DEFINITION

Folic Acid Oral Solution is a solution of Folic Acid Hydrate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of folic acid, $C_{19}H_{19}N_7O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the oral solution containing the equivalent of 20 mg of folic acid with sufficient of a mixture of 2 volumes of 13.5M *ammonia* and 9 volumes of *methanol* to produce 100 mL.

(2) 0.02% w/v of *folic acid BPCRS* in a mixture of 2 volumes of 13.5M *ammonia* and 9 volumes of *methanol*.

(3) Equal volumes of solution (1) and solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel 60* pre-coated plate (Merck TLC silica gel 60 is suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (365 nm)*.

MOBILE PHASE

20 volumes of 13.5M*ammonia* and 20 volumes of *propan-1-ol* and 60 volumes of *ethanol (96%)*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) appears as a single compact spot.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 5.5 to 6.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) To a quantity of the oral solution containing the equivalent of 2.5 mg of folic acid, add 2.5 mL of a 2.86% w/v solution of *sodium carbonate* and dilute to 50 mL with mobile phase A. Dilute 10 volumes of this solution to 25 volumes with the same solvent.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of this solution to 5 volumes with the same solvent.
(3) Dilute 1 volume of a solution containing 0.0008% w/v of *folic acid impurity A EPCRS* and 0.00024% of *folic acid impurity D EPCRS* in a 2.86% w/v solution of *sodium carbonate*, to 20 volumes with mobile phase A.
(4) Dilute 1 volume of a solution containing 0.0001% w/v of *folic acid EPCRS* and 0.001% w/v of *folic acid impurity D EPCRS* in a 2.86% w/v solution of *sodium carbonate*, to 20 volumes with mobile phase A.
(5) Dissolve 5 mg of *folic acid for system suitability EPCRS* (containing impurities C, E, G and H) in 10 mL of a 2.86% w/v solution of *sodium carbonate* and dilute to 25 mL with mobile phase A. Dilute 1 volume of this solution to 10 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Merck Lichrospher 100 RP 8 is suitable).
(b) Use isocratic elution for solutions (2) to (4) and gradient elution for solution (1) (to elute any peaks due to the sample matrix) and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use an ambient column temperature. Maintain the auto-sampler at 10°.
(e) Use a detection wavelength of 280 nm.
(f) Inject 25 µL of each solution.

MOBILE PHASE

Mobile phase A 10 volumes of *methanol* and 90 volumes of a solution containing 1.116 w/v% of *potassium dihydrogen phosphate* and 0.55% w/v of *dipotassium hydrogen phosphate*.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-45	100	0	isocratic

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
45-46	100→50	0→50	linear gradient
46-70	50	50	isocratic
70-71	50→100	50→0	linear gradient
71-85	100	0	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to folic acid and impurity D is at least 4.0.

When the chromatograms are recorded under the prescribed conditions, the approximate retention time relative to folic acid (retention time, about 8.5 minutes) are: impurity A, about 0.5; impurity C, about 0.9; impurity E, about 1.3, impurity D, about 1.5 and impurity G, about 2.4.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (2%);

the area of any peak due to impurity D is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.6%);

the area of any peak due to impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak due to impurity E is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak due to impurity G is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of all impurities is not greater than 3.0%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) To a weighed quantity of the oral solution containing 2.5mg of *folic acid* add 2.5 mL of a 2.86% w/v solution of *sodium carbonate*, dilute to 50 mL with the mobile phase and filter. Dilute 10 volumes of this solution to 25 volumes with mobile phase A.

www.webofpharma.com

https://thietbiuocngocanh.com/

(2) Dilute 10 volumes of a 0.1% w/v solution of *folic acid BPCRS* in a 2.86% w/v solution of *sodium carbonate* to 25 volumes with the mobile phase.

(3) Dilute 1 volume of a solution containing 0.0002% w/v of *folic acid EPCRS* and 0.002% w/v of *folic acid impurity D EPCRS* in a 2.86% w/v solution of *sodium carbonate*, to 20 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under related substances may be used, with an injection volume of 10 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to folic acid and impurity D is at least 4.0.

DETERMINATION OF CONTENT

Determine the weight per mL of the oral solution, Appendix V G, and calculate the content of $C_{19}H_{19}N_7O_6$, weight in volume, using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Folic Acid Hydrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Folic Acid Tablets

General Notices

Action and use

Vitamin B component.

DEFINITION

Folic Acid Tablets contain Folic Acid Hydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of folic acid, $C_{19}H_{19}N_7O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing the equivalent of 0.5 mg of folic acid with 1 mL of a mixture of 1 volume of 13.5M *ammonia* and 9 volumes of *methanol*, centrifuge and use the supernatant liquid.

(2) 0.05% w/v of *folic acid BPCRS* in a mixture of 2 volumes of 13.5M *ammonia* and 9 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (365 nm)*.

MOBILE PHASE

20 volumes of 13.5M *ammonia*, 20 volumes of *propan-1-ol* and 60 volumes of *ethanol (96%)*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, fluorescence and size to that in the chromatogram obtained with solution (2).

TESTS

Hydrolysis products

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the powdered tablets containing the equivalent of 5.0 mg of folic acid with 50 mL of the mobile phase, centrifuge and use the supernatant liquid.
(2) 0.00005% w/v of *4-aminobenzoic acid* and 0.0002% w/v of N-*(4-aminobenzoyl)*-L-*glutamic acid* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 269 nm.
(f) Inject 20 µL of each solution.

In the chromatogram obtained with solution (2) the substances elute in the following order: *N*-(4-aminobenzoyl)-L-glutamic acid and 4-aminobenzoic acid.

MOBILE PHASE

0.05M *potassium dihydrogen orthophosphate*, adjusted to pH 5.5 with 5M *sodium hydroxide*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the two peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the areas of the peaks corresponding to 4-aminobenzoic acid and *N*-(4-aminobenzoyl)-L-glutamic acid are not greater than the areas of the peaks corresponding to 4-aminobenzoic acid and *N*-(4-aminobenzoyl)-L-glutamic acid in the chromatogram obtained with solution (2) (0.5% and 2% respectively).

Uniformity of content

Tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake one tablet with 5 mL of 0.1M *sodium hydroxide*, add sufficient mobile phase to produce a solution containing the equivalent of 0.001% w/v of folic acid, centrifuge and use the supernatant liquid.
(2) Add 1 mL of 0.5M *hydrochloric acid* to 5 mL of a 0.0020% w/v solution of *folic acid BPCRS* in 0.1M *sodium hydroxide* and dilute to 10 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 283 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

7 volumes of *acetonitrile* and 93 volumes of 0.05M *potassium dihydrogen orthophosphate* adjusted to pH 6.0 with 5M *sodium hydroxide*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in each tablet using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of folic acid

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

(1) Shake a quantity of the powdered tablets containing the equivalent of 20 mg of folic acid with 50 mL of 0.1M *sodium hydroxide*, dilute to 100 mL with the same solvent, centrifuge and dilute 5 mL of the supernatant liquid to 100 mL with the mobile phase.

(2) Dilute 5 mL of a 0.020% w/v solution of *folic acid BPCRS* in 0.1M *sodium hydroxide* to 100 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in the tablets using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

STORAGE

Folic Acid Tablets should be protected from light.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Follitropin

General Notices

(Ph. Eur. monograph 2285)

α-subunit

```
APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP    40
LRSKKTMLVQ KNVTSESTCC VAKSYNRVTV MGGFKVENHT    80
ACHCSTCYYH KS                                  92
```

β-subunit

```
NSCELTNITI AIEKEECRFC ISINTTWCAG YCYTRDLVYK   40'
DPARPKIQKT CTFKELVYET VRVPGCAHHA DSLYTYPVAT   80'
QCHCGKCDSD STDCTVRGLG PSYCSFGEMK E           111'
```

glycosylation sites:
Asn-52, Asn-78, Asn-7', Asn-24'

disulfide bridges:
7-31, 10-60, 28-82, 32-84, 59-87, 3'-51', 17'-66', 20'-104', 28'-82', 32'-84', 87'-94'

M_r approx. 30 000 - 40 000

Action and use

Recombinant human follicle stimulating hormone; treatment of female infertility.

Ph Eur

DEFINITION

Freeze-dried preparation of a heterodimeric glycoprotein having the structure of human follicle-stimulating hormone (FSH). It consists of 2 subunits: a 92-amino-acid α-chain common to other glycoprotein hormones and a specific 111-amino-acid β-chain.

Potency

9000 IU to 17 000 IU per milligram of protein.

PRODUCTION

Follitropin is produced in mammalian cells by a method based on recombinant DNA (rDNA) technology.

Follitropin complies with the following requirements.

Host-cell-derived proteins

https://thuocngocanh.com/

The limit is approved by the competent authority.

Host-cell- and vector-derived DNA

The limit is approved by the competent authority.

CHARACTERS

Appearance

White or almost white powder.

IDENTIFICATION

A. It complies with the requirements described under Assay.

B. Isoelectric focusing (2.2.54).

Test solution Dissolve the substance to be examined in *water R* to obtain a concentration of about 2 mg/mL, then desalt and concentrate using a suitably validated procedure. Reconstitute the recovered material in *water R* to obtain a concentration of 5 mg/mL.

Reference solution Dissolve the contents of a vial of *follitropin CRS* in *water R* to obtain a concentration of 5 mg/mL.

Focusing:

— *pH gradient*: a combination of ampholytes and electrode buffers giving a functional separation in the isoelectric point (pI) range of 3.5-5.5 is selected, as defined by the system suitability criteria; where pre-cast gels are employed, proprietary electrode solutions may be used in conjunction; otherwise, suitable dilute mineral or organic acids and bases are employed at pH levels respectively lower and higher than the functional range of the ampholytes;

— *catholyte*: 20.0 g/L solution of *glycine R*;

— *anolyte*: solution containing 3.4 g/L of *aspartic acid R* and 3.6 g/L of *glutamic acid R*, adjusted to pH 2.8-3.8;

— *application*: 10 µL.

Detection: as described in 2.2.54.

System suitability:

— in the electropherogram obtained with the reference solution, the number of bands seen in the pI region 3.5-5.5 corresponds to that shown in the electropherogram supplied with *follitropin CRS*; the distribution of bands in the pI region 3.5-5.5 is qualitatively similar to that shown in the electropherogram supplied with *follitropin CRS*.

Results Examine the electropherogram obtained with the test solution; identify the bands observed by comparison with the electropherogram obtained with the reference solution; the pattern of bands is qualitatively similar to that seen with the reference solution.

C. Examine the chromatograms obtained in the test for follitropin oligomers.

www.webofpharma.com

https://thuocngocanh.com/

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

D. Peptide mapping (2.2.55).

SEPARATION OF THE α- AND β-SUBUNITS Liquid chromatography (2.2.29).

Test solution Dissolve the substance to be examined in mobile phase A to obtain a concentration of about 0.4 mg/mL.

Reference solution Dilute *follitropin for peptide mapping and glycan analysis CRS* with mobile phase A to obtain a concentration of about 0.4 mg/mL.

Precolumn:

— *size*: *l* = 0.012 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm.

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *trifluoroacetic acid R*, *water for chromatography R*, *acetonitrile for chromatography R* (0.9:50:950 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 8	100 → 76	0 → 24
8 - 17	76	24
17 - 36	76 → 70	24 → 30
36 - 41	70 → 25	30 → 75
41 - 46	25	75
46 - 47	25 → 100	75 → 0
47 - 57	100	0

Flow rate 1.0 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 226 nm.

Injection 800 µL.

Retention time β-subunit = about 14 min; α-subunit = about 30 min.

Collect the fractions containing the α- and β-subunits and freeze-dry them.

REDUCTION, MODIFICATION AND DESALTING OF THE PURIFIED SUBUNITS

Reduction and modification

Solution A Dilute 10 µL of *tributylphosphine R* to 2 mL with *propanol R*. Saturate with nitrogen.

Solution B Dilute 20 µL of *4-vinylpyridine R* to 200 µL with *propanol R*. Saturate with nitrogen.

Test solutions Dissolve each of the α- and β-subunit fractions obtained from the test solution in the previous step in 300 µL of *guanidine-tris(hydroxymethyl)aminomethane-EDTA buffer solution pH 8.5 R* and incubate at 37 °C for 60 min in a thermostatically controlled water-bath. Add 100 µL of solution A, mix and saturate with nitrogen. Incubate at 37 °C for 90 min. Add 10 µL of solution B, mix and saturate with nitrogen. Incubate at 37 °C for 45 min. Add 100 µL of a 10 per cent *V/V* solution of *trifluoroacetic acid R* and mix.

Reference solutions Prepare at the same time and in the same manner as for the test solutions but using the α- and β-subunit fractions obtained from the reference solution in the previous step.

Desalting

Dilute the α- and β-subunit test and reference solutions to 840 µL with mobile phase A.

Column:

— *size*: *l* = 0.02 m, Ø = 4.6 mm;

— *stationary phase*: *butylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *trifluoroacetic acid R*, *water for chromatography R*, *acetonitrile for chromatography R* (1:300:700 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	100	0
7 - 27	100 → 0	0 → 100
27 - 27.01	0 → 100	100 → 0
27.01 - 32	100	0

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 226 nm.

Injection 800 µL.

For each solution the chromatogram shows a principal peak due to the monovinylpyridine-modified subunit and several minor peaks due to the di- and oligovinylpyridine-modified subunits. Only the fraction containing the monovinylpyridine-modified subunit is used for digestion in the following step.

Retention time *α-subunit solution*: monovinylpyridine-modified α-subunit = about 15 min; *β-subunit solution*: monovinylpyridine-modified β-subunit = about 16 min.

Collect the fractions containing the monovinylpyridine-modified subunits and freeze-dry them.

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Solution C (8 M urea solution). Dissolve 480 g of *urea R* in 600 mL of *water for chromatography R* and dilute to 1000 mL with the same solvent. Add about 3-5 g of mixed-bed resin and stir for about 1 h. Filter through a glass filter before use.

Solution D Dissolve 15.8 g of *ammonium hydrogen carbonate R* and 8.3 g of *sodium edetate R* in 800 mL of *water for chromatography R*. Adjust to pH 7.8 (*2.2.3*) with an 80 g/L solution of *sodium hydroxide R* and dilute to 1000 mL with *water for chromatography R*.

Test solutions Dissolve each of the modified α- and β-subunits obtained from the test solutions in the previous step in 42.5 µL of solution C and incubate at room temperature for 30 min. Add 42.5 µL of solution D and mix. To 42.5 µL of these solutions add 35 µL of a solution containing about 23 mU/µL of endoproteinase Lys-C and mix. Incubate at 37 °C for 4 h, then add 35 µL of the same endoproteinase Lys-C solution and mix. Incubate at 37 °C overnight, then dilute to 420 µL with mobile phase A.

Reference solutions Prepare at the same time and in the same manner as for the test solutions but using the fractions obtained from the reference solutions in the previous step.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (*2.2.29*).

Precolumn:

— *size*: *l* = 0.02 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *trifluoroacetic acid R*, *water for chromatography R*, *acetonitrile R1* (1:300:700 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	100	0
7 - 77	100 → 30	0 → 70
77 - 82	30 → 0	70 → 100
82 - 87	0	100
87 - 92	0 → 100	100 → 0
92 - 107	100	0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 400 µL.

System suitability:

α-subunit:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of follitropin α-subunit digest supplied with *follitropin for peptide mapping and glycan analysis CRS*; both chromatograms show peaks due to the L4, L6, L3, L5 and L1-2/L1 fragments;

— retention times obtained with the test and reference solutions differ by not more than 5 per cent for fragments L4, L6 and L3, not more than 3 per cent for fragment L5 and not more than 2 per cent for fragments L1-2/L1;

β-subunit:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of follitropin β-subunit digest supplied with *follitropin for peptide mapping and glycan analysis CRS*; both chromatograms show peaks due to the L5, L7, L6, and L1-4 fragments;

— retention times obtained with the test and reference solutions differ by not more than 5 per cent for fragment L5, not more than 2 per cent for fragments L7 and L6 and not more than 1 per cent for fragments L1-4.

Results For each subunit, the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the corresponding reference solution.

E. Glycan analysis (*2.2.59*). Carry out either method A or method B.

www.webofpharma.com

https://thuocngocanh.com/

METHOD A

PROTEIN DENATURATION

Test solution Dissolve 500 µg of the substance to be examined in 60 µL of *0.05 M phosphate buffer solution pH 7.5 R*. Add 6 µL of a 10 mg/mL solution of *sodium dodecyl sulfate R* and 35 µL of a 1 per cent *V/V* solution of *2-mercaptoethanol R*. Mix using a vortex mixer, centrifuge and incubate at 37 °C for 15 min.

Reference solution Freeze dry a sample of *follitropin for peptide mapping and glycan analysis CRS* that contains 500 µg of follitropin. Dissolve in 60 µL of *0.05 M phosphate buffer solution pH 7.5 R* and continue as for the test solution.

SELECTIVE RELEASE OF THE GLYCANS

Test solution To the test solution obtained in the previous step add 0.75 µL of octylphenyl-polyethylene glycol and mix using a vortex mixer. Add 25 mU of *peptide N-glycosidase F R*, mix using a vortex mixer and centrifuge. Incubate at 37 °C for 24 h. Remove the protein fraction using a suitable, validated procedure. The following method has been found to be appropriate. Add 600 µL of *anhydrous ethanol R*, previously cooled at -20 °C for 45 min. Mix using a vortex mixer and centrifuge. Precipitate the proteins at -20 °C for 15 min, then centrifuge at 10 600 *g* at 4 °C for 5 min. Transfer the supernatant to a separate tube and evaporate the ethanol for 15 min. Add 1 mL of *particle-free water R* and resume evaporating until the remaining volume is about 500-800 µL, then freeze-dry.

Label the liberated glycans contained in the sample with 2-aminobenzamide. The procedure employs a combination of reagents optimised and validated for the efficient labelling of glycans, and for the subsequent extraction and recovery of the labelled glycans from the reaction. Recover the sample in 1.5 mL of *particle-free water R*.

Reference solution Prepare at the same time and in the same manner as for the test solution but using the reference solution obtained in the previous step.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (*2.2.29*).

Column:

— *size*: *l* = 0.075 m, Ø = 7.5 mm;

— *stationary phase*: *weak anion-exchange resin R* (10 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*;

— *mobile phase B*: *0.5 M ammonium acetate buffer solution pH 4.5 R*; filter through a membrane filter (nominal pore size 0.22 µm);

— *mobile phase C*: *particle-free water R*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 5	20	0	80
5 - 21	20	0 → 4	80 → 76
21 - 61	20	4 → 25	76 → 55
61 - 62	20	25 → 50	55 → 30
62 - 71	20	50	30
71 - 72	20	50 → 0	30 → 80
72 - 117	20	0	80

Flow rate 0.4 mL/min.

Detection Fluorimeter at 330 nm for excitation and at 420 nm for emission.

Injection 50 µL.

System suitability Reference solution:

— the chromatogram obtained is qualitatively similar to the chromatogram supplied with *follitropin for peptide mapping and glycan analysis CRS*;

— by comparison with the chromatogram supplied with *follitropin for peptide mapping and glycan analysis CRS*, identify the peaks due to neutral, mono-, di-, tri- and tetra-sialylated forms; determine the area of each peak and express it as a percentage of the total; calculate the *Z* number using the following expression:

$$\left(A_0 \times 0\right) + \left(A_1 \times 1\right) + \left(A_2 \times 2\right) + \left(A_3 \times 3\right) + \left(A_4 \times 4\right)$$

A_0 = peak area percentage due to the neutral form;

A_1 = peak area percentage due to the mono-sialylated form;

A_2 = peak area percentage due to the di-sialylated form;

A_3 = peak area percentage due to the tri-sialylated form;

A_4 = peak area percentage due to the tetra-sialylated form.

The *Z* number obtained for the reference solution is in the range 177-233.

Examine the chromatogram obtained with the test solution and calculate the *Z* number as described above.

Result *Z* = 177-233.

www.webofpharma.com

https://thuocngocanh.com/

METHOD B

PROTEIN DENATURATION

Solution A To 1.952 g of *2-[N-morpholino]ethanesulfonic acid R* and 57.32 g of *guanidine hydrochloride R*, add 1 mL of a 15.4 g/L solution of *dithiothreitol R*, 10 mL of an 18.61 g/L solution of *sodium edetate R* and 20 mL of *water for chromatography R*. Maintain in a water-bath at about 37 °C for 1 min to dissolve the components. Adjust to pH 8.1 (*2.2.3*) with an 80 g/L solution of *sodium hydroxide R* and dilute to 100.0 mL with *water for chromatography R*. Mix.

Solution B Dissolve 37 mg of *iodoacetamide R* in 1 mL of *water for chromatography R* and mix. Protect from light.

Solution C Dissolve 26.7 g of *disodium hydrogen phosphate dihydrate R* and 11.2 g of *sodium edetate R* in 3000 mL of *water for chromatography R* and mix. Adjust to pH 7.5 (*2.2.3*) with a 40 g/L solution of *sodium hydroxide R*.

Test solution Dissolve 1 mg of the substance to be examined in 0.2 mL of solution A and incubate in a water-bath at 37 ± 1 °C for 2 h. Add 20 µL of freshly prepared solution B, mix and incubate at 37 ± 1 °C for a further 2 h, protected from light. Add 10 µL of *2-mercaptoethanol R* and mix. Dialyse against 1000 mL of solution C. Add 200 µL of solution C and mix. Determine the protein content of the solution.

Reference solution (a) To a volume of *follitropin for peptide mapping and glycan analysis CRS* that contains 1 mg of follitropin, add 0.2 mL of solution A. Incubate in a water-bath at 37 ± 1 °C for 2 h. Continue as for the test solution. Determine the protein content of the solution.

Reference solution (b) Prepare at the same time and in the same manner as for the test solution but using fetuin instead of the substance to be examined. Determine the protein content of the solution.

SELECTIVE RELEASE OF THE GLYCANS

Test solution Dilute the test solution obtained in the previous step with solution C to obtain a concentration of 1.1 g/L. Add 1 U of *peptide N-glycosidase F R* to 500 µg of the solution, mix and incubate at 37 ± 1 °C for 24 h. Place the solution in ice. Precipitate the protein and salts with 3 volumes of ice-cold *anhydrous ethanol R* and allow to stand in ice for 10 min. Centrifuge at 16 000 *g* for about 5 min and transfer the supernatant to a separate tube. Add 3 µL of a 1 µg/µL solution of *maltotriose R*, then freeze-dry. Dissolve in 100 µL of *water for chromatography R*.

Reference solution (a) Prepare in the same manner as for the test solution but using the reference solution obtained with *follitropin for peptide mapping and glycan analysis CRS* in the previous step.

Reference solution (b) Prepare in the same manner as for the test solution but using the reference solution obtained with fetuin in the previous step.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (*2.2.29*).

Precolumn:

— *size*: *l* = 0.05 m, Ø = 4.0 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R*;

www.webofpharma.com

https://thuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *strongly basic anion-exchange resin for chromatography R*.

Mobile phase:

— *mobile phase A*: 20 g/L solution of *sodium hydroxide R*; maintain under helium;

— *mobile phase B*: *water for chromatography R*; maintain under helium;

— *mobile phase C*: dissolve 41 g of *anhydrous sodium acetate R* in 800 mL of *water for chromatography R*, dilute to 1000 mL with the same solvent, then mix; filter through a membrane filter (nominal pore size 0.45 µm); maintain under helium;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 0.2	20	80	0
0.2 - 94.0	20	80 → 34	0 → 46
94.0 - 97.0	20	34	46
97.0 - 97.1	20	34 → 80	46 → 0
97.1 - 115.0	20	80	0

Flow rate 1.0 mL/min.

Detection Pulsed amperometric detector or equivalent with a gold indicator electrode, a silver-silver chloride reference electrode, and a stainless steel auxiliary electrode which is the cell body, held at respectively + 0.05 V detection, + 0.75 V oxidation and -0.80 V reduction potentials, with pulse durations according to the instrument used.

Injection 45 µL.

System suitability:

— the chromatogram obtained with reference solution (b) is qualitatively similar to the chromatogram for fetuin supplied with *follitropin for peptide mapping and glycan analysis CRS*;

— the chromatograms obtained with the test solution and reference solution (a) are qualitatively similar to the chromatogram supplied with *follitropin for peptide mapping and glycan analysis CRS*;

— by comparison with the chromatogram supplied with *follitropin for peptide mapping and glycan analysis CRS*, identify the peaks due to neutral, mono-, di-, tri- and tetra-sialylated forms in the chromatogram obtained with reference solution (b); determine the area of each peak and express it as a percentage of the total; calculate the *Z* number using the following expression:

$$\left(A_0 \times 0\right) + \left(A_1 \times 1\right) + \left(A_2 \times 2\right) + \left(A_3 \times 3\right) + \left(A_4 \times 4\right)$$

www.webofpharma.com

https://thuocngocanh.com/

A_0 = peak area percentage due to the neutral form;

A_1 = peak area percentage due to the mono-sialylated form;

A_2 = peak area percentage due to the di-sialylated form;

A_3 = peak area percentage due to the tri-sialylated form;

A_4 = peak area percentage due to the tetra-sialylated form.

The *Z* number obtained for reference solution (b) is in the range 290-325.

Examine the chromatogram obtained with the test solution and calculate the *Z* number as described above.

Result *Z* = 178-274.

TESTS

Follitropin oligomers

Size-exclusion chromatography (2.2.30). Use the normalisation procedure.

Solution A Dissolve 118 mg of *sodium dihydrogen phosphate R*, 1.65 g of *disodium hydrogen phosphate dihydrate R* and 30.0 g of *sucrose R* in 40 mL of *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Solution B Dissolve 2.0 mg of *bovine albumin R* in 30 mL of solution A.

Test solution Dissolve the substance to be examined in solution A to obtain a concentration of 0.25 mg/mL.

Reference solution Dissolve the contents of a vial of *follitropin CRS* in solution A to obtain a concentration of 0.5 mg/mL and mix equal volumes of this solution and solution B to obtain a concentration of 0.25 mg/mL.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R*, of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 10 000 to 300 000 (5 µm).

Mobile phase Dissolve 28.4 g of *anhydrous sodium sulfate R* in 2000 mL of *0.1 M phosphate buffer solution pH 6.7 R* and filter through a membrane filter (nominal pore size 0.45 µm).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 100 µL.

Retention time Follitropin = 14-16 min.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution:

— *resolution*: minimum 1.2 between the peaks due to bovine albumin and follitropin;

— no peak is detected between 5 min and 16 min in blank injections.

Limit:

— *sum of the peaks with a retention time less than that of the principal peak*: maximum 0.5 per cent.

Free subunits

Polyacrylamide gel electrophoresis (2.2.31) under non-reducing conditions.

Gel dimensions 1.5 mm thick.

Resolving gel 12 per cent acrylamide.

Sample buffer *Concentrated SDS-PAGE sample buffer R*.

Test solution Dissolve the substance to be examined in *water R* to obtain a concentration of 2 µg/µL. To 55 µL of the solution add 55 µL of the sample buffer. Allow to stand for 4 h at room temperature.

Reference solution (a) Dissolve the contents of a vial of *follitropin CRS* in *water R* to obtain a concentration of 2 µg/µL. To 25 µL of the solution add 25 µL of the sample buffer. To 40 µL of this solution add 180 µL of the sample buffer and 180 µL of *water R*. Allow to stand for 4 h at room temperature, then boil for 5 min.

Reference solution (b) A solution of molecular mass markers suitable for calibrating SDS-polyacrylamide gels in the range of 14.4-94 kDa.

Application:

Well	Solution(s)	Volume (µL)
1	Reference solution (a)	40
2	Reference solution (a)	30
3	Reference solution (a)	20
4	Reference solution (a)	15
5	Reference solution (a)	10
6	Reference solution (a)	5
7	Test solution	50
8	Test solution + reference solution (a)	50 + 25
9	Reference solution (b)	10

www.webofpharma.com

https://thuocngocanh.com/

Detection By Coomassie staining.

System suitability:

— reference solution (b): the validation criteria are met (2.2.31);

— test solution + reference solution (a): the bands corresponding to the follitropin heterodimer and subunits are clearly separated;

— reference solution (a): no bands corresponding to the follitropin heterodimer are seen.

Limit:

— *free subunits*: maximum 3 per cent.

Oxidised follitropin

Liquid chromatography (2.2.29).

Solution A Dissolve about 3.3 mg of 2,4-dichlorobenzoic acid R in 10.0 mL of ethanol (96 per cent) R.

Test solution Dissolve the substance to be examined in water for chromatography R to obtain a concentration of 300 µg/mL.

Reference solution (a) Dissolve the contents of a vial of follitropin CRS in water for chromatography R to obtain a concentration of 300 µg/mL.

Reference solution (b) Dilute 0.1 mL of strong hydrogen peroxide solution R to 30 mL with water for chromatography R. Dissolve the contents of a vial of follitropin CRS in this solution to obtain a concentration of 300 µg/mL. Incubate for 30-45 min. Add solution A to obtain a concentration in 2,4-dichlorobenzoic acid of about 17 µg/mL in the total volume and inject immediately.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped butylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 0.2 M phosphate buffer solution pH 2.5 R;

— *mobile phase B*: water for chromatography R, acetonitrile R1 (40:60 *V/V*);

— *mobile phase C*: water for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 8.4	50	25 → 39	25 → 11

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
8.4 - 8.5	50	39 → 45	11 → 5
8.5 - 15	50	45	5
15 - 15.1	50	45 → 25	5 → 25
15.1 - 25	50	25	25

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 25 µL.

Identification of peaks Use the chromatogram supplied with *follitropin CRS* and the chromatogram obtained with reference solutions (a) and (b) to identify the peaks due to non-oxidised and oxidised follitropin subunits and to 2,4-dichlorobenzoic acid.

System suitability Reference solution (b):

— the peaks due to the oxidised follitropin α- and β-subunits are separated from the peaks due to the non-oxidised follitropin subunits and from the peak due to 2,4-dichlorobenzoic acid;

— the chromatogram obtained is qualitatively similar to the chromatogram supplied with *follitropin CRS*.

Calculate the percentage of oxidation of the follitropin subunits using the following expression:

$$\frac{(A_2 + A_4) \times 100}{A_1 + A_2 + A_3 + A_4}$$

A_1 = area of the peak due to the non-oxidised follitropin α-subunit;

A_2 = area of the peaks (potentially 3) due to the oxidised follitropin α-subunit;

A_3 = area of the peak due to the non-oxidised follitropin β-subunit;

A_4 = area of the peak due to the oxidised follitropin β-subunit.

Limit:

— *total oxidised forms*: maximum 6 per cent.

Bacterial endotoxins (*2.6.14*)

Less than 0.1 IU per International Unit of follitropin activity, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Protein

Size-exclusion chromatography (2.2.30).

Solution A Dissolve 100 mg of poloxamer 188 R in 900 mL of water for chromatography R and dilute to 1000 mL with the same solvent.

Test solution Dissolve the substance to be examined in solution A to obtain a concentration of about 0.03 mg/mL.

Reference solution Dissolve the contents of a vial of follitropin CRS in solution A to obtain a concentration of about 0.03 mg/mL.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: hydrophilic silica gel for chromatography R, of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 10 000 to 300 000 (5 µm).

Mobile phase Mix 6.74 mL of phosphoric acid R, 14.2 g of anhydrous sodium sulfate R and 900 mL of water for chromatography R, adjust to pH 6.7 (2.2.3) with a 0.5 g/mL solution of sodium hydroxide R and dilute to 1000 mL with water for chromatography R; filter through a membrane filter (nominal pore size 0.45 µm).

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 100 µL.

System suitability Reference solution:

— number of theoretical plates: minimum 1300, calculated for the peak due to follitropin.

Calculate the content of follitropin taking into account the assigned content of follitropin CRS.

Potency

The follicle-stimulating activity of follitropin is estimated by comparing under given conditions its effect in enlarging the ovaries of immature rats treated with chorionic gonadotrophin with the same effect of the International Standard preparation of human recombinant follicle-stimulating hormone or of a reference preparation calibrated in International Units. The International Unit of FSH is the activity contained in stated amounts of the International Standard of human recombinant follicle-stimulating hormone. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Use immature female rats of the same strain, 19-28 days old, differing in age by not more than 3 days and having masses such that the difference between the heaviest and the lightest rat is not more than 10 g. Assign the rats at random to 6 equal groups of at least 5 rats. If sets of 6 litter mates are available, assign 1 litter mate from each set to each group and mark according to litter.

Choose 3 doses of the reference preparation and 3 doses of the preparation to be examined such that the smallest dose produces a positive response in some of the rats and the largest dose does not produce a maximal response in all of the rats. Use doses in geometric

www.webofpharma.com

https://thuocngocanh.com/

progression and as an initial approximation total doses of 1.5 IU, 3.0 IU and 6.0 IU may be tried, although the dose will depend on the sensitivity of the rats used, which may vary widely.

Dissolve separately the total quantities of the preparation to be examined and of the reference preparation corresponding to the daily doses to be used in sufficient *phosphate-albumin buffered saline pH 7.2 R* such that the daily dose is administered in a volume of about 0.5 mL. The buffer solution shall contain in the daily dose not less than 14 IU of chorionic gonadotrophin to ensure complete luteinisation. Add a suitable antimicrobial preservative such as 4 g/L of phenol or 0.02 g/L of thiomersal. Store the solutions at 5 ± 3 °C.

Inject subcutaneously into each rat the daily dose allocated to its group. Repeat the injection of each dose 24 h and 48 h after the 1st injection. About 24 h after the last injection, euthanise the rats and remove the ovaries from each rat. Remove any extraneous fluid and tissue from the ovaries and weigh the 2 combined ovaries of each rat immediately. Calculate the results by the usual statistical methods (for example, *5.3*), using the mass of the 2 combined ovaries as the response (a suitable correction of the organ mass with reference to the mass of the rat from which it was taken may be applied; an analysis of covariance may be used).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) of the estimated potency are not less than 64 per cent and not more than 156 per cent of the stated potency.

STORAGE

In an airtight container, at a temperature not exceeding -20 °C.

LABELLING

The label states:

— the potency in International Units per milligram of protein;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Follitropin Concentrated Solution

General Notices

(Ph. Eur. monograph 2286)

α-subunit

```
APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP     40
LRSKKTMLVQ KNVTSESTCC VAKSYNRVTV MGGFKVENHT     80
ACHCSTCYYH KS                                   92
```

β-subunit

```
NSCELTNITI AIEKEECRFC ISINTTWCAG YCYTRDLVYK    40'
DPARPKIQKT CTFKELVYET VRVPGCAHHA DSLYTYPVAT    80'
QCHCGKCDSD STDCTVRGLG PSYCSFGEMK E            111'
```

glycosylation sites:
Asn-52, Asn-78, Asn-7', Asn-24'

disulfide bridges:
7-31, 10-60, 28-82, 32-84, 59-87, 3'-51', 17'-66', 20'-104', 28'-82', 32'-84', 87'-94'

M_r approx. 30 000 - 40 000

Action and use

Recombinant human follicle stimulating hormone; treatment of female infertility.

Ph Eur

DEFINITION

Solution of a heterodimeric glycoprotein having the structure of human follicle-stimulating hormone (FSH). It consists of 2 subunits: a 92-amino-acid α-chain common to other glycoprotein hormones and a specific 111-amino-acid β-chain.

Content

0.4 mg to 0.8 mg of protein per millilitre.

Potency

9000 IU to 17 000 IU per milligram of protein.

PRODUCTION

www.webofpharma.com

https://thuocngocanh.com/

Follitropin is produced in mammalian cells by a method based on recombinant DNA (rDNA) technology.

Follitropin complies with the following requirements.

Host-cell-derived proteins

The limit is approved by the competent authority.

Host-cell- and vector-derived DNA

The limit is approved by the competent authority.

CHARACTERS

Appearance

Clear or slightly turbid, colourless liquid.

IDENTIFICATION

A. It complies with the requirements described under Assay.

B. Isoelectric focusing (2.2.54).

Test solution Desalt and concentrate the preparation to be examined using a suitably validated procedure. Reconstitute the recovered material in *water R* to obtain a concentration of 5 mg/mL.

Reference solution Dissolve the contents of a vial of *follitropin CRS* in *water R* to obtain a concentration of 5 mg/mL.

Focusing:

— *pH gradient*: a combination of ampholytes and electrode buffers giving a functional separation in the isoelectric point (pI) range of 3.5-5.5 is selected, as defined by the system suitability criteria; where pre-cast gels are employed, proprietary electrode solutions may be used in conjunction; otherwise, suitable dilute mineral or organic acids and bases are employed at pH levels respectively lower and higher than the functional range of the ampholytes;

— *catholyte*: 20.0 g/L solution of *glycine R*;

— *anolyte*: solution containing 3.4 g/L of *aspartic acid R* and 3.6 g/L of *glutamic acid R*, adjusted to pH 2.8-3.8;

— *application*: 10 µL.

Detection As described in 2.2.54.

System suitability:

— in the electropherogram obtained with the reference solution, the number of bands seen in the pI region 3.5-5.5 corresponds to that shown in the electropherogram supplied with *follitropin CRS*; the distribution of bands in the pI region 3.5-5.5 is qualitatively similar to that shown in the electropherogram supplied with *follitropin CRS*.

www.webofpharma.com

https://thuocngocanh.com/

Results Examine the electropherogram obtained with the test solution; identify the bands observed by comparison with the electropherogram obtained with the reference solution; the pattern of bands is qualitatively similar to that seen with the reference solution.

C. Examine the chromatograms obtained in the test for follitropin oligomers.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

D. Peptide mapping (2.2.55).

SEPARATION OF THE α- AND β-SUBUNITS Liquid chromatography (2.2.29).

Test solution Dilute the preparation to be examined with mobile phase A to obtain a concentration of about 0.4 mg/mL.

Reference solution Dilute *follitropin for peptide mapping and glycan analysis CRS* with mobile phase A to obtain a concentration of about 0.4 mg/mL

Precolumn:

— *size*: *l* = 0.012 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm) with a pore size of 30 nm.

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *trifluoroacetic acid R*, *water for chromatography R*, *acetonitrile for chromatography R* (0.9:50:950 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 8	100 → 76	0 → 24
8 - 17	76	24
17 - 36	76 → 70	24 → 30
36 - 41	70 → 25	30 → 75
41 - 46	25	75
46 - 47	25 → 100	75 → 0

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
47 - 57	100	0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 226 nm.

Injection 800 µL.

Retention time B-subunit = about 14 min; α-subunit = about 30 min.

Collect the fractions containing the α- and β-subunits and freeze-dry them.

REDUCTION, MODIFICATION AND DESALTING OF THE PURIFIED SUBUNITS

Reduction and modification

Solution A Dilute 10 µL of *tributylphosphine R* to 2 mL with *propanol R*. Saturate with nitrogen.

Solution B Dilute 20 µL of *4-vinylpyridine R* to 200 µL with *propanol R*. Saturate with nitrogen.

Test solutions Dissolve each of the α- and β-subunit fractions obtained from the test solution in the previous step in 300 µL of *guanidine-tris(hydroxymethyl)aminomethane-EDTA buffer solution pH 8.5 R* and incubate at 37 °C for 60 min in a thermostatically controlled water-bath. Add 100 µL of solution A, mix and saturate with nitrogen. Incubate at 37 °C for 90 min. Add 10 µL of solution B, mix and saturate with nitrogen. Incubate at 37 °C for 45 min. Add 100 µL of a 10 per cent *V/V* solution of *trifluoroacetic acid R* and mix.

Reference solutions Prepare at the same time and in the same manner as for the test solutions but using the α- and β-subunit fractions obtained from the reference solution in the previous step.

Desalting

Dilute the α- and β-subunit test and reference solutions to 840 µL with mobile phase A.

Column:

— *size*: *l* = 0.02 m, Ø = 4.6 mm;

— *stationary phase*: *butylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dilute 1 mL of *trifluoroacetic acid R* to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *trifluoroacetic acid R*, *water for chromatography R*, *acetonitrile for chromatography R* (1:300:700 *V/V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	100	0
7 - 27	100 → 0	0 → 100
27 - 27.01	0 → 100	100 → 0
27.01 - 32	100	0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 226 nm.

Injection 800 µL.

For each solution the chromatogram shows a principal peak due to the monovinylpyridine-modified subunit and several minor peaks due to the di- and oligovinylpyridine-modified subunits. Only the fraction containing the monovinylpyridine-modified subunit is used for digestion in the following step.

Retention time *α-subunit solution*: monovinylpyridine-modified α-subunit = about 15 min; *β-subunit solution*: monovinylpyridine-modified β-subunit = about 16 min.

Collect the fractions containing the monovinylpyridine-modified subunits and freeze-dry them.

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Solution C (8 M urea solution). Dissolve 480 g of *urea R* in 600 mL of *water for chromatography R* and dilute to 1000 mL with the same solvent. Add about 3-5 g of mixed-bed resin and stir for about 1 h. Filter through a glass filter before use.

Solution D Dissolve 15.8 g of *ammonium hydrogen carbonate R* and 8.3 g of *sodium edetate R* in 800 mL of *water for chromatography R*. Adjust to pH 7.8 (*2.2.3*) with an 80 g/L solution of *sodium hydroxide R* and dilute to 1000 mL with *water for chromatography R*.

Test solutions Dissolve each of the modified α- and β-subunits obtained from the test solutions in the previous step in 42.5 µL of solution C and incubate at room temperature for 30 min. Add 42.5 µL of solution D and mix. To 42.5 µL of these solutions add 35 µL of a solution containing about 23 mU/µL of endoproteinase Lys-C and mix. Incubate at 37 °C for 4 h, then add 35 µL of the same endoproteinase Lys-C solution and mix. Incubate at 37 °C overnight, then dilute to 420 µL with mobile phase A.

Reference solutions Prepare at the same time and in the same manner as for the test solutions but using the fractions obtained from the reference solutions in the previous step.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (*2.2.29*).

Precolumn:

www.webofpharma.com

https://thietbiluocngocanh.com/

— *size*: *l* = 0.02 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm) with a pore size of 30 nm.

Mobile phase:

— *mobile phase A*: dilute 1 mL of trifluoroacetic acid R to 1000 mL with water for chromatography R;

— *mobile phase B*: trifluoroacetic acid R, water for chromatography R, acetonitrile R1 (1:300:700 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	100	0
7 - 77	100 → 30	0 → 70
77 - 82	30 → 0	70 → 100
82 - 87	0	100
87 - 92	0 → 100	100 → 0
92 - 107	100	0

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 400 µL.

System suitability:

α-subunit:

— the chromatogram obtained with the reference solution is qualitatively similar to the chromatogram of follitropin α-subunit digest supplied with follitropin for peptide mapping and glycan analysis CRS; both chromatograms show peaks due to the L4, L6, L3, L5 and L1-2/L1 fragments;

— retention times obtained with the test and reference solutions differ by not more than 5 per cent for fragments L4, L6 and L3, not more than 3 per cent for fragment L5 and not more than 2 per cent for fragments L1-2/L1;

β-subunit:

www.webofpharma.com

https://thuocngocanh.com/

— the chromatogram obtained with the reference solutions is qualitatively similar to the chromatogram of follitropin β-subunit digest supplied with *follitropin for peptide mapping and glycan analysis CRS*; both chromatograms show peaks due to the L5, L7, L6, and L1-4 fragments;

— retention times obtained with the test and reference solutions differ by not more than 5 per cent for fragment L5, not more than 2 per cent for fragments L7 and L6 and not more than 1 per cent for fragments L1-4.

Results For each subunit, the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the corresponding reference solution.

E. Glycan analysis (*2.2.59*). Carry out either method A or method B.

METHOD A

PROTEIN DENATURATION

Test solution Freeze-dry a sample of the preparation to be examined that contains 500 µg of follitropin. Dissolve in 60 µL of *0.05 M phosphate buffer solution pH 7.5 R*. Add 6 µL of a 10 mg/mL solution of *sodium dodecyl sulfate R* and 35 µL of a 1 per cent *V/V* solution of *2-mercaptoethanol R*. Mix using a vortex mixer, centrifuge and incubate at 37 °C for 15 min.

Reference solution Prepare at the same time and in the same manner as for the test solution but using *follitropin for peptide mapping and glycan analysis CRS* instead of the freeze-dried preparation to be examined.

SELECTIVE RELEASE OF THE GLYCANS

Test solution To the test solution obtained in the previous step add 0.75 µL of octylphenyl-polyethylene glycol and mix using a vortex mixer. Add 25 mU of *peptide N-glycosidase F R*, mix using a vortex mixer and centrifuge. Incubate at 37 °C for 24 h. Remove the protein fraction using a suitable, validated procedure. The following method has been found to be appropriate. Add 600 µL of *anhydrous ethanol R*, previously cooled at -20 °C for 45 min. Mix using a vortex mixer and centrifuge. Precipitate the proteins at -20 °C for 15 min, then centrifuge at 10 600 *g* at 4 °C for 5 min. Transfer the supernatant to a separate tube and evaporate the ethanol for 15 min. Add 1 mL of *particle-free water R* and resume evaporating until the remaining volume is about 500-800 µL, then freeze-dry.

Label the liberated glycans contained in the sample with 2-aminobenzamide. The procedure employs a combination of reagents optimised and validated for the efficient labelling of glycans, and for the subsequent extraction and recovery of the labelled glycans from the reaction. Recover the sample in 1.5 mL of *particle-free water R*.

Reference solution Prepare at the same time and in the same manner as for the test solution but using the reference solution obtained in the previous step.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (*2.2.29*).

Column:

— *size*: *l* = 0.075 m, Ø = 7.5 mm;

— *stationary phase*: *weak anion-exchange resin R* (10 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile R*;

— *mobile phase B*: *0.5 M ammonium acetate buffer solution pH 4.5 R*; filter through a membrane filter (nominal pore size 0.22 µm);

— *mobile phase C*: *particle-free water R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 5	20	0	80
5 - 21	20	0 → 4	80 → 76
21 - 61	20	4 → 25	76 → 55
61 - 62	20	25 → 50	55 → 30
62 - 71	20	50	30
71 - 72	20	50 → 0	30 → 80
72 - 117	20	0	80

Flow rate 0.4 mL/min.

Detection Fluorimeter at 330 nm for excitation and at 420 nm for emission.

Injection 50 µL.

System suitability Reference solution:

— the chromatogram obtained is qualitatively similar to the chromatogram supplied with *follitropin for peptide mapping and glycan analysis CRS*;

— by comparison with the chromatogram supplied with *follitropin for peptide mapping and glycan analysis CRS*, identify the peaks due to neutral, mono-, di-, tri- and tetra-sialylated forms; determine the area of each peak and express it as a percentage of the total; calculate the *Z* number using the following expression:

$$\left(A_0 \times 0\right) + \left(A_1 \times 1\right) + \left(A_2 \times 2\right) + \left(A_3 \times 3\right) + \left(A_4 \times 4\right)$$

A_0 = peak area percentage due to the neutral form;

A_1 = peak area percentage due to the mono-sialylated form;

A_2 = peak area percentage due to the di-sialylated form;

www.webofpharma.com

https://thuocngocanh.com/

A_3 = peak area percentage due to the tri-sialylated form;

A_4 = peak area percentage due to the tetra-sialylated form.

The *Z* number obtained for the reference solution is in the range 177-233.

Examine the chromatogram obtained with the test solution and calculate the *Z* number as described above.

Result *Z* = 177-233.

METHOD B

PROTEIN DENATURATION

Solution A To 1.952 g of *2-[N-morpholino]ethanesulfonic acid R* and 57.32 g of *guanidine hydrochloride R*, add 1 mL of a 15.4 g/L solution of *dithiothreitol R*, 10 mL of an 18.61 g/L solution of *sodium edetate R* and 20 mL of *water for chromatography R*. Maintain in a water-bath at about 37 °C for 1 min to dissolve the components. Adjust to pH 8.1 (*2.2.3*) with an 80 g/L solution of *sodium hydroxide R* and dilute to 100.0 mL with *water for chromatography R*. Mix.

Solution B Dissolve 37 mg of *iodoacetamide R* in 1 mL of *water for chromatography R* and mix. Protect from light.

Solution C Dissolve 26.7 g of *disodium hydrogen phosphate dihydrate R* and 11.2 g of *sodium edetate R* in 3000 mL of *water for chromatography R* and mix. Adjust to pH 7.5 (*2.2.3*) with a 40 g/L solution of *sodium hydroxide R*.

Test solution To a volume of the preparation to be examined that contains 1 mg of follitropin add 0.2 mL of solution A and incubate in a water-bath at 37 ± 1 °C for 2 h. Add 20 µL of freshly prepared solution B, mix and incubate at 37 ± 1 °C for a further 2 h, protected from light. Add 10 µL of *2-mercaptoethanol R* and mix. Dialyse against 1000 mL of solution C. Add 200 µL of solution C and mix. Determine the protein content of the solution.

Reference solution (a) Prepare at the same time and in the same manner as for the test solution but using *follitropin for peptide mapping and glycan analysis CRS* instead of the preparation to be examined. Determine the protein content of the solution.

Reference solution (b) Prepare at the same time and in the same manner as for the test solution but using fetuin instead of the preparation to be examined. Determine the protein content of the solution.

SELECTIVE RELEASE OF THE GLYCANS

Test solution Dilute the test solution obtained in the previous step with solution C to obtain a concentration of 1.1 g/L. Add 1 U of *peptide N-glycosidase F R* to 500 µg of the solution, mix and incubate at 37 ± 1 °C for 24 h. Place the solution in ice. Precipitate the protein and salts with 3 volumes of ice-cold *anhydrous ethanol R* and allow to stand in ice for 10 min. Centrifuge at 16 000 *g* for about 5 min and transfer the supernatant to a separate tube. Add 3 µL of a 1 µg/µL solution of *maltotriose R* then freeze-dry. Dissolve in 100 µL of *water for chromatography R*.

Reference solution (a) Prepare in the same manner as for the test solution but using the reference solution obtained with *follitropin for peptide mapping and glycan analysis CRS* in the previous step.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Prepare in the same manner as for the test solution but using the reference solution obtained with fetuin in the previous step.

CHROMATOGRAPHIC SEPARATION

Liquid chromatography (2.2.29).

Precolumn:

— *size*: *l* = 0.05 m, Ø = 4.0 mm;

— *stationary phase*: strongly basic anion-exchange resin for chromatography R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: strongly basic anion-exchange resin for chromatography R.

Mobile phase:

— *mobile phase A*: 20 g/L solution of sodium hydroxide R; maintain under helium;

— *mobile phase B*: water for chromatography R; maintain under helium;

— *mobile phase C*: dissolve 41 g of anhydrous sodium acetate R in 800 mL of water for chromatography R, dilute to 1000 mL with the same solvent, then mix; filter through a membrane filter (nominal pore size 0.45 µm); maintain under helium;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 0.2	20	80	0
0.2 - 94.0	20	80 → 34	0 → 46
94.0 - 97.0	20	34	46
97.0 - 97.1	20	34 → 80	46 → 0
97.1 - 115.0	20	80	0

Flow rate 1.0 mL/min.

Detection Pulsed amperometric detector or equivalent with a gold indicator electrode, a silver-silver chloride reference electrode, and a stainless steel auxiliary electrode which is the cell body, held at respectively + 0.05 V detection, + 0.75 V oxidation and -0.80 V reduction potentials, with pulse durations according to the instrument used.

Injection 45 µL.

System suitability:

www.webofpharma.com

https://thuocngocanh.com/

— the chromatogram obtained with reference solution (b) is qualitatively similar to the chromatogram for fetuin supplied with *follitropin for peptide mapping and glycan analysis CRS*;

— the chromatograms obtained with the test solution and reference solution (a) are qualitatively similar to the chromatogram supplied with *follitropin for peptide mapping and glycan analysis CRS*;

— by comparison with the chromatogram supplied with *follitropin for peptide mapping and glycan analysis CRS*, identify the peaks due to neutral, mono-, di-, tri- and tetra-sialylated forms in the chromatogram obtained with reference solution (b); determine the area of each peak and express it as a percentage of the total; calculate the *Z* number using the following expression:

$$\left(A_0 \times 0\right) + \left(A_1 \times 1\right) + \left(A_2 \times 2\right) + \left(A_3 \times 3\right) + \left(A_4 \times 4\right)$$

A_0 = peak area percentage due to the neutral form;

A_1 = peak area percentage due to the mono-sialylated form;

A_2 = peak area percentage due to the di-sialylated form;

A_3 = peak area percentage due to the tri-sialylated form;

A_4 = peak area percentage due to the tetra-sialylated form.

The *Z* number obtained for reference solution (b) is in the range 290-325.

Examine the chromatogram obtained with the test solution and calculate the *Z* number as described above.

Result *Z* = 178-274.

TESTS

Follitropin oligomers

Size-exclusion chromatography (*2.2.30*). Use the normalisation procedure.

Solution A Dissolve 118 mg of *sodium dihydrogen phosphate R*, 1.65 g of *disodium hydrogen phosphate dihydrate R*, and 30.0 g of *sucrose R* in 40 mL of *water for chromatography R* and dilute to 100.0 mL with the same solvent.

Solution B Dissolve 2.0 mg of *bovine albumin R* in 30 mL of solution A.

Test solution Dilute the preparation to be examined with solution A to obtain a concentration of 0.25 mg/mL.

Reference solution Dissolve the contents of a vial of *follitropin CRS* in solution A to obtain a concentration of 0.5 mg/mL and mix equal volumes of this solution and solution B to obtain a concentration of 0.25 mg/mL.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *hydrophilic silica gel for chromatography R*, of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 10 000 to 300 000 (5 µm).

Mobile phase Dissolve 28.4 g of *anhydrous sodium sulfate R* in 2000 mL of *0.1 M phosphate buffer solution pH 6.7 R* and filter through a membrane filter (nominal pore size 0.45 µm).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 100 µL.

Retention time Follitropin = 14-16 min.

System suitability Reference solution:

— *resolution*: minimum 1.2 between the peaks due to bovine albumin and follitropin;

— no peak is detected between 5 min and 16 min in blank injections.

Limit:

— *sum of the peaks with a retention time less than that of the principal peak*: maximum 0.5 per cent.

Free subunits

Polyacrylamide gel electrophoresis (*2.2.31*) under non-reducing conditions.

Gel dimensions 1.5 mm thick.

Resolving gel 12 per cent acrylamide.

Sample buffer *Concentrated SDS-PAGE sample buffer R*.

Test solution Dilute the preparation to be examined with *water R* to obtain a concentration of 2 µg/µL. To 55 µL of the solution add 55 µL of the sample buffer. Allow to stand for 4 h at room temperature.

Reference solution (a) Dissolve the contents of a vial of *follitropin CRS* in *water R* to obtain a concentration of 2 µg/µL. To 25 µL of the solution add 25 µL of the sample buffer. To 40 µL of this solution add 180 µL of the sample buffer and 180 µL of *water R*. Allow to stand for 4 h at room temperature, then boil for 5 min.

Reference solution (b) A solution of molecular mass markers suitable for calibrating SDS-polyacrylamide gels in the range of 14.4-94 kDa.

Application:

Well	Solution(s)	Volume (µL)
1	Reference solution (a)	40

www.webofpharma.com

https://thuocngocanh.com/

Well	Solution(s)	Volume (µL)
2	Reference solution (a)	30
3	Reference solution (a)	20
4	Reference solution (a)	15
5	Reference solution (a)	10
6	Reference solution (a)	5
7	Test solution	50
8	Test solution + reference solution (a)	50 + 25
9	Reference solution (b)	10

Detection By Coomassie staining.

System suitability:

— reference solution (b): the validation criteria are met (2.2.31);

— test solution + reference solution (a): the bands corresponding to the follitropin heterodimer and subunits are clearly separated;

— reference solution (a): no bands corresponding to the follitropin heterodimer are seen.

Limit:

— *free subunits*: maximum 3 per cent.

Oxidised follitropin

Liquid chromatography (2.2.29).

Solution A Dissolve about 3.3 mg of *2,4-dichlorobenzoic acid R* in 10.0 mL of *ethanol (96 per cent) R*.

Test solution Dilute the preparation to be examined in *water for chromatography R* to obtain a concentration of 300 µg/mL.

Reference solution (a) Dissolve the contents of a vial of *follitropin CRS* in *water for chromatography R* to obtain a concentration of 300 µg/mL.

Reference solution (b) Dilute 0.1 mL of *strong hydrogen peroxide solution R* to 30 mL with *water for chromatography R*. Dissolve the contents of a vial of *follitropin CRS* in this solution to obtain a concentration of 300 µg/mL. Incubate for 30-45 min. Add solution A to obtain a concentration in 2,4-dichlorobenzoic acid of about 17 µg/mL in the total volume and inject immediately.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *end-capped butylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *0.2 M phosphate buffer solution pH 2.5 R*;

— *mobile phase B*: *water for chromatography R*, *acetonitrile R1* (40:60 *V/V*);

— *mobile phase C*: *water for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Mobile phase C (per cent *V/V*)
0 - 8.4	50	25 → 39	25 → 11
8.4 - 8.5	50	39 → 45	11 → 5
8.5 - 15	50	45	5
15 - 15.1	50	45 → 25	5 → 25
15.1 - 25	50	25	25

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 25 µL.

Identification of peaks Use the chromatogram supplied with *follitropin CRS* and the chromatogram obtained with reference solutions (a) and (b) to identify the peaks due to non-oxidised and oxidised follitropin subunits and to 2,4-dichlorobenzoic acid.

System suitability Reference solution (b):

— the peaks due to the oxidised follitropin α- and β-subunits are separated from the peaks due to the non-oxidised follitropin subunits and from the peak due to 2,4-dichlorobenzoic acid;

— the chromatogram obtained is qualitatively similar to the chromatogram supplied with *follitropin CRS*.

Calculate the percentage of oxidation of the follitropin subunits using the following expression:

$$\frac{(A_2 + A_4) \times 100}{A_1 + A_2 + A_3 + A_4}$$

A_1 = area of the peak due to the non-oxidised follitropin α-subunit;

A_2 = area of the peaks (potentially 3) due to the oxidised follitropin α-subunit;

www.webofpharma.com

https://thuocngocanh.com/

A_3 = area of the peak due to the non-oxidised follitropin β-subunit;

A_4 = area of the peak due to the oxidised follitropin β-subunit.

Limit:

— *total oxidised forms*: maximum 6 per cent.

Bacterial endotoxins (2.6.14)

Less than 0.1 IU per International Unit of follitropin activity, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Protein

Size-exclusion chromatography (2.2.30).

Solution A Dissolve 100 mg of *poloxamer 188 R* in 900 mL of *water for chromatography R* and dilute to 1000 mL with the same solvent.

Test solution Dilute the preparation to be examined with solution A to obtain a concentration of about 0.03 mg/mL.

Reference solution Dissolve the contents of a vial of *follitropin CRS* in solution A to obtain a concentration of about 0.03 mg/mL.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *hydrophilic silica gel for chromatography R*, of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 10 000 to 300 000 (5 µm).

Mobile phase Mix 6.74 mL of *phosphoric acid R*, 14.2 g of *anhydrous sodium sulfate R* and 900 mL of *water for chromatography R*, adjust to pH 6.7 (2.2.3) with a 0.5 g/mL solution of *sodium hydroxide R* and dilute to 1000 mL with *water for chromatography R*; filter through a membrane filter (nominal pore size 0.45 µm).

Flow rate 1 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 100 µL.

System suitability Reference solution:

— *number of theoretical plates*: minimum 1300, calculated for the peak due to follitropin.

Calculate the content of follitropin taking into account the assigned content of *follitropin CRS*.

Potency

www.webofpharma.com

https://thuocngocanh.com/

The follicle-stimulating activity of follitropin is estimated by comparing under given conditions its effect in enlarging the ovaries of immature rats treated with chorionic gonadotrophin with the same effect of the International Standard preparation of human recombinant follicle-stimulating hormone or of a reference preparation calibrated in International Units. The International Unit of FSH is the activity contained in stated amounts of the International Standard of human recombinant follicle-stimulating hormone. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Use immature female rats of the same strain, 19-28 days old, differing in age by not more than 3 days and having masses such that the difference between the heaviest and the lightest rat is not more than 10 g. Assign the rats at random to 6 equal groups of at least 5 rats. If sets of 6 litter mates are available, assign 1 litter mate from each set to each group and mark according to litter.

Choose 3 doses of the reference preparation and 3 doses of the preparation to be examined such that the smallest dose produces a positive response in some of the rats and the largest dose does not produce a maximal response in all of the rats. Use doses in geometric progression and as an initial approximation total doses of 1.5 IU, 3.0 IU and 6.0 IU may be tried, although the dose will depend on the sensitivity of the rats used, which may vary widely.

Dilute and dissolve respectively the total quantities of the preparation to be examined and of the reference preparation corresponding to the daily doses to be used in sufficient *phosphate-albumin buffered saline pH 7.2 R* such that the daily dose is administered in a volume of about 0.5 mL. The buffer solution shall contain in the daily dose not less than 14 IU of chorionic gonadotrophin to ensure complete luteinisation. Add a suitable antimicrobial preservative such as 4 g/L of phenol or 0.02 g/L of thiomersal. Store the solutions at 5 ± 3 °C.

Inject subcutaneously into each rat the daily dose allocated to its group. Repeat the injection of each dose 24 h and 48 h after the 1st injection. About 24 h after the last injection, euthanise the rats and remove the ovaries from each rat. Remove any extraneous fluid and tissue from the ovaries and weigh the 2 combined ovaries of each rat immediately. Calculate the results by the usual statistical methods (for example, *5.3*), using the mass of the 2 combined ovaries as the response (a suitable correction of the organ mass with reference to the mass of the rat from which it was taken may be applied; an analysis of covariance may be used).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits (P = 0.95) of the estimated potency are not less than 64 per cent and not more than 156 per cent of the stated potency.

STORAGE

In an airtight container, at a temperature not exceeding -20 °C.

LABELLING

The label states:

— the content of protein in milligrams per millilitre;

— the potency in International Units per milligram of protein;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Formaldehyde Solution

General Notices

Formalin

(Formaldehyde Solution (35 per cent), Ph. Eur. monograph 0826)

NOTE: *The name Formalin as a synonym for Formaldehyde Solution may be used freely in many countries, including the United Kingdom, but in other countries exclusive proprietary rights in this name are claimed.*

50-00-0

Action and use

When suitably diluted, used in the treatment of warts.

Ph Eur

DEFINITION

Content

34.5 per cent *m/m* to 38.0 per cent *m/m* of formaldehyde (CH_2O; M_r 30.03).

It contains methanol as stabiliser.

CHARACTERS

Appearance

Clear, colourless liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

It may be cloudy after storage.

IDENTIFICATION

A. Dilute 1 mL of solution S (see Tests) to 10 mL with *water R*. To 0.05 mL of the solution add 1 mL of a 15 g/L solution of *chromotropic acid, sodium salt R*, 2 mL of *water R* and 8 mL of *sulfuric acid R*. A violet-blue or violet-red colour develops within 5 min.

B. To 0.1 mL of solution S add 10 mL of *water R*. Add 2 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R*, prepared immediately before use, 1 mL of *potassium ferricyanide solution R* and 5 mL of *hydrochloric acid R*. An intense red colour is formed.

www.webofpharma.com

https://thuocngocanh.com/

C. Mix 0.5 mL with 2 mL of *water R* and 2 mL of *silver nitrate solution R2* in a test-tube. Add *dilute ammonia R2* until slightly alkaline. Heat on a water-bath. A grey precipitate or a silver mirror is formed.

D. It complies with the limits of the assay.

TESTS

Solution S

Dilute 10 mL, filtered if necessary, to 50 mL with *carbon dioxide-free water R*.

Appearance of solution

Solution S is colourless (*2.2.2, Method II*).

Acidity

To 10 mL of solution S add 1 mL of *phenolphthalein solution R*. Not more than 0.4 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to red.

Methanol

Gas chromatography (*2.2.28*).

Internal standard solution Dilute 10 mL of *ethanol R1* to 100 mL with *water R*.

Test solution To 10.0 mL of the solution to be examined add 10.0 mL of the internal standard solution and dilute to 100.0 mL with *water R*.

Reference solution To 1.0 mL of *methanol R* add 10.0 mL of the internal standard solution and dilute to 100.0 mL with *water R*.

Column:

— *material*: glass,

— *size*: *l* = 1.5-2.0 m, Ø = 2-4 mm,

— *stationary phase*: *ethylvinylbenzene-divinylbenzene copolymer R* (150-180 µm).

Carrier gas *nitrogen for chromatography R*.

Flow rate 30-40 mL/min.

Temperature:

— *column*: 120 °C,

— *injection port and detector*: 150 °C.

Detection Flame ionisation.

www.webofpharma.com

https://thuocngocanh.com/

Injection 1 µL of the test solution and the reference solution.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to methanol and ethanol.

Limit:

— *methanol*: 9.0 per cent *V/V* to 15.0 per cent *V/V*.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Into a 100 mL volumetric flask containing 2.5 mL of *water R* and 1 mL of *dilute sodium hydroxide solution R*, introduce 1.000 g of the solution to be examined, shake and dilute to 100.0 mL with *water R*. To 10.0 mL of the solution add 30.0 mL of *0.05 M iodine*. Mix and add 10 mL of *dilute sodium hydroxide solution R*. After 15 min, add 25 mL of *dilute sulfuric acid R* and 2 mL of *starch solution R*. Titrate with *0.1 M sodium thiosulfate*.

1 mL of *0.05 M iodine* is equivalent to 1.501 mg of CH_2O.

STORAGE

Protected from light, at a temperature of 15 °C to 25 °C.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

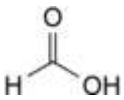
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Formic Acid

General Notices

(Ph. Eur. monograph 2809)



CH_2O_2 46.03 *64-18-6*

Ph Eur

DEFINITION

Content

98.0 per cent *m/m* to 100.5 per cent *m/m*.

CHARACTERS

Appearance

Clear, colourless, volatile liquid.

Solubility

Miscible with water, with ethanol (96 per cent) and with methylene chloride.

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Films.

Comparison *formic acid CRS*.

B. A 100 g/L solution is strongly acid (*2.2.4*).

C. To 2.0 mL of *dilute sodium hydroxide solution R* add 0.05 mL of *phenolphthalein solution R*. Mix, and add dropwise the substance to be examined until the solution becomes colourless. To 1 mL of this solution add 0.5 mL of *silver nitrate solution R2* and mix. Initially no change

www.webofpharma.com

https://thuocngocanh.com/

occurs. Slowly (quicker upon heating), the solution turns greyish and turbid due to the precipitation of metallic silver.

D. To the remainder of the neutralised solution obtained in identification test C, add 0.5 mL of *ferric chloride solution R1*. The solution turns orange-red or brownish-red.

TESTS

Solution S

Extract the residue obtained in the test for residue on evaporation by heating with 2 quantities, each of 15 mL, of *distilled water R*. After cooling, dilute the combined extracts to 50.0 mL with *distilled water R*.

Appearance

The substance to be examined is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Relative density (*2.2.5*)

1.217 to 1.223.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dilute 0.500 g of the substance to be examined to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 0.500 g of *anhydrous acetic acid R* (impurity A) to 100.0 mL with the mobile phase. Mix 2.0 mL of the solution and 1.0 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (4 µm).

Mobile phase 2.72 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 2.9 with *dilute phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 3 times the retention time of formic acid.

Relative retention With reference to formic acid (retention time = about 3 min): impurity A = about 1.5.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to formic acid and impurity A.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides (2.4.4)

Maximum 10 ppm.

Dilute 12.5 mL of solution S to 15 mL with *water R*.

Sulfates (2.4.13)

Maximum 50 ppm.

Dilute 7.5 mL of solution S to 15 mL with *distilled water R*.

Sulfites

Maximum 300 ppm.

To 0.5 mL add 12.0 mL of a 42 g/L solution of *sodium hydroxide R* in *carbon dioxide-free water R* and mix. Upon addition of 0.5 mL of *iodine solution R1* and 0.2 mL of *starch solution R* the solution remains blue.

Residue on evaporation

Maximum 0.01 per cent.

Condensing the vapour where possible, evaporate 20.0 g to dryness on a water-bath and dry at 105 °C. The residue weighs a maximum of 2.0 mg. The residue is used for the preparation of solution S.

ASSAY

Weigh accurately a conical flask with a ground-glass stopper containing 20 mL of *water R*. Add 1.0 mL of the substance to be examined and weigh again accurately. Titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20).

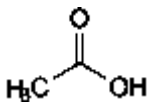
1 mL of *1 M sodium hydroxide* is equivalent to 46.03 mg of CH_2O_2.

IMPURITIES

www.webofpharma.com

https://thuvienthuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A.



A. acetic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

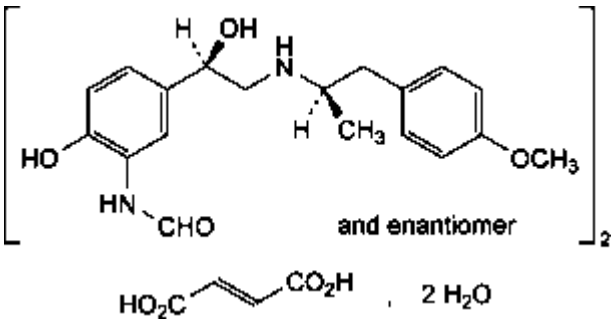
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Formoterol Fumarate Dihydrate

General Notices

(Ph. Eur. monograph 1724)



$C_{42}H_{52}N_4O_{12},2H_2O$ 841 *183814-30-4*

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

Ph Eur

DEFINITION

N-[2-Hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]phenyl]formamide (2*E*)-but-2-enedioate dihydrate.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white or slightly yellow powder.

Solubility

Slightly soluble in water, soluble in methanol, slightly soluble in 2-propanol, practically insoluble in acetonitrile.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *formoterol fumarate dihydrate CRS*.

TESTS

pH (2.2.3)

5.5 to 6.5.

Dissolve 20 mg in *carbon dioxide-free water R* while heating to about 40 °C, allow to cool and dilute to 20 mL with the same solvent.

Optical rotation (2.2.7)

-0.10° to + 0.10°.

Dissolve 0.25 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solution A Dissolve 6.10 g of *sodium dihydrogen phosphate monohydrate R* and 1.03 g of *disodium hydrogen phosphate dihydrate R* in *water R* and dilute to 1000 mL with the same solvent. The pH is 6.0 ± 0.1.

Solvent mixture *acetonitrile R*, solution A (16:84 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture. *Inject within 4 h of preparation, or within 24 h if stored protected from light at 4 °C.*

Reference solution (a) Dissolve 5 mg of *formoterol for system suitability CRS* (containing impurities A, C and F) in the solvent mixture and dilute to 25 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R1*;

— *mobile phase B*: dissolve 3.73 g of *sodium dihydrogen phosphate monohydrate R* and 0.35 g of *phosphoric acid R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; the pH is 3.1 ± 0.1;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	16	84
10 - 37	16 → 70	84 → 30

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL; inject the solvent mixture until a repeatable profile is obtained.

Identification of impurities Use the chromatogram obtained with reference solution (a) and the chromatogram supplied with *formoterol for system suitability CRS* to identify the peaks due to impurities A, C and F.

Relative retention With reference to formoterol (retention time = about 12 min): fumaric acid = about 0.1; impurity A = about 0.5; impurity C = about 1.2; impurity F = about 2.0.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to formoterol.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 1.75;

— for each impurity, use the concentration of formoterol fumarate dihydrate in reference solution (b).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *impurity F*: maximum 0.15 per cent for the sum of the areas of the isomer peaks;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak due to fumaric acid.

Impurity I

Liquid chromatography (*2.2.29*).

Test solution Dissolve 5.0 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent. Sonicate if necessary.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dissolve 5 mg of *formoterol for impurity I identification CRS* in *water R* and dilute to 50 mL with the same solvent. Sonicate if necessary.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with *water R*. Dilute 1.0 mL of this solution to 25.0 mL with *water R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl vinyl polymer for chromatography R* (5 µm).

Mobile phase Mix 12 volumes of *acetonitrile for chromatography R* with 88 volumes of a 5.3 g/L solution of *tripotassium phosphate trihydrate R* previously adjusted to pH 12.0 ± 0.1 with a 280 g/L solution of *potassium hydroxide R* or *phosphoric acid R*.

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *formoterol for impurity I identification CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity I.

Relative retention With reference to formoterol (retention time = about 20 min): impurity I = about 1.2.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to formoterol.

Calculation of percentage content:

— for impurity I, use the concentration of formoterol fumarate dihydrate in reference solution (b).

Limit:

— *impurity I*: maximum 0.3 per cent.

Water (*2.5.12*)

4.0 per cent to 5.0 per cent, determined on 0.100 g.

ASSAY

Dissolve 0.350 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 40.24 mg of $C_{42}H_{52}N_4O_{12}$.

www.webofpharma.com

https://thuocngocanh.com/

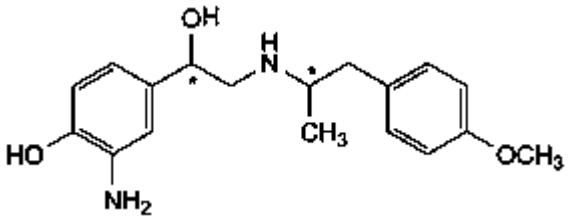
STORAGE

Protected from light.

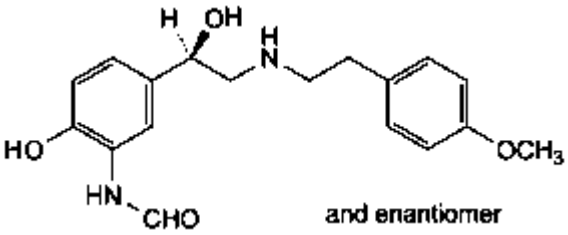
IMPURITIES

Specified impurities A, F, I.

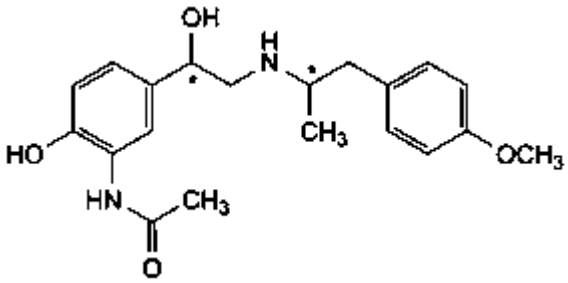
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, G, H.



A. 2-amino-4-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]phenol,



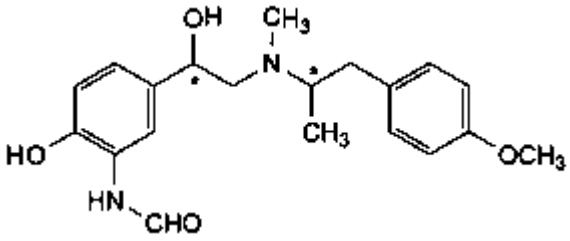
B. *N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]phenyl]formamide,



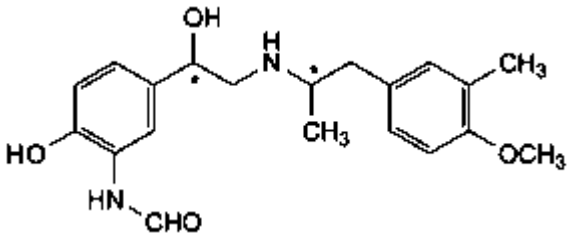
C. *N*-[2-hydroxy-5-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]phenyl]acetamide,

www.webofpharma.com

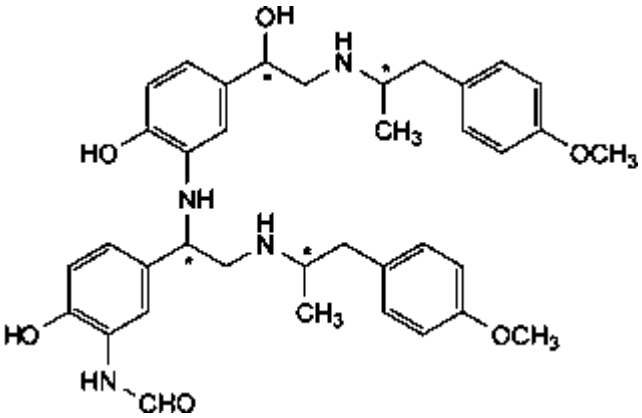
https://thuocngocanh.com/



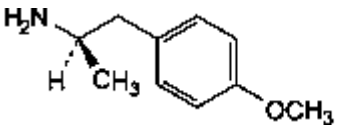
D. *N*-[2-hydroxy-5-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-1-(4-methoxyphenyl)propan-2-yl](methyl)amino]ethyl]phenyl]formamide,



E. *N*-[2-hydroxy-5-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-1-(4-methoxy-3-methylphenyl)propan-2-yl]amino]ethyl]phenyl]formamide,

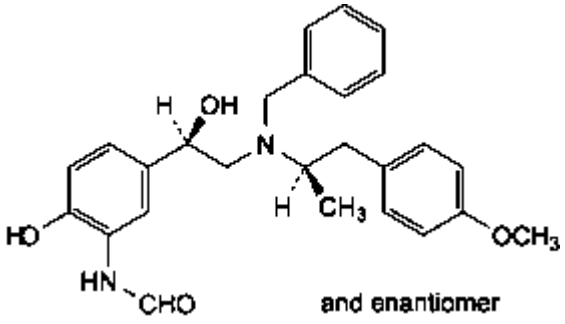


F. *N*-[2-hydroxy-5-[(1Ξ)-1-[[2-hydroxy-5-[(1Ξ)-1-hydroxy-2-[[(2Ξ)-1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]phenyl]amino]-2-[[(2Ξ)-1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]phenyl]formamide,



and enantiomer

G. (2*RS*)-1-(4-methoxyphenyl)propan-2-amine,

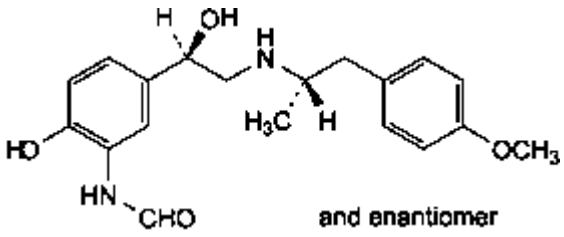


and enantiomer

H. *N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[benzyl[(2*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]phenyl]formamide,

www.webofpharma.com

https://thuocngocanh.com/



and enantiomer

I. *N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(2*SR*)-1-(4-methoxyphenyl)propan-2-yl]amino]ethyl]phenyl]formamide.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Foscarnet Infusion

General Notices

Foscarnet Intravenous Infusion

Action and use

Antiviral (cytomegalovirus).

DEFINITION

Foscarnet Infusion is a sterile solution containing Foscarnet Sodium. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of foscarnet sodium, $CNa_3O_5P,6H_2O$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A clear, colourless solution.

IDENTIFICATION

A. Dry a quantity of the infusion containing 48 mg of Foscarnet Sodium over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa for 16 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of foscarnet sodium *(RS 160)*. Disregard any peak occurring at 902 cm^{-1} or any shoulder at 1179 cm^{-1}.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH, 7.2 to 7.6, Appendix V L.

Phosphate and phosphite

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.04% w/v of *sodium dihydrogen orthophosphate monohydrate* and 0.06% w/v of *sodium phosphite*.

www.webofpharma.com

https://thuocngocanh.com/

(1) Dilute a volume of the infusion with sufficient *water* to produce a solution containing 0.24% w/v of Foscarnet Sodium.

(2) Add 6 mL of solution A to 60 mg of *foscarnet sodium BPCRS* and dilute to 25 mL with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 4.6 mm) packed with *anion-exchange resin* (Waters IC PAK is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.4 mL per minute.

(d) Use a column temperature of 25°.

(e) Use a detection wavelength of 290 nm (indirect detection).

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of phosphite.

MOBILE PHASE

Dissolve 0.204 g of *potassium hydrogen phthalate* in *water*, adding 5 mL of 1M *nitric acid VS* and sufficient *water* to produce 2000 mL.

Allow the column to stabilise by passing mobile phase through it for at least 2 hours before starting the chromatography.

When the chromatograms are recorded under the prescribed conditions, the retention time of phosphate is about 4 minutes and the retention time of phosphite is about 5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks due to phosphate and phosphite is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to phosphate is not greater than 0.7 times the area of the corresponding peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to phosphite is not greater than half the area of the corresponding peak in the chromatogram obtained with solution (2) (1.0%).

Related esters

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a volume of the infusion with sufficient mobile phase to produce a solution containing 1.0% w/v of Foscarnet Sodium.

(2) Dilute 1 volume of solution (1) to 500 volumes.

(3) 0.02% w/v of *foscarnet sodium BPCRS* and 0.02% w/v of *foscarnet impurity B BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Microsphere C18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 230 nm.

(f) Inject 5 µL of each solution.

(g) Allow the chromatography to proceed for 2.5 times the retention time of foscarnet.

MOBILE PHASE

Prepare two solutions containing (A) 100 mL of 0.5M *acetic acid*, 6 mL of 0.1M *sodium pyrophosphate* and 3.22 g of *sodium sulfate* in sufficient *water* to produce 1000 mL and (B) 6.8 g of *sodium acetate*, 6 mL of 0.1M *sodium pyrophosphate* and 3.22 g of *sodium sulfate* in sufficient *water* to produce 1000 mL.

Mix solution A and solution B to produce a solution of pH 4.4 and to 1000 mL of this solution add 0.25 g of *tetrahexylammonium hydrogen sulfate* and 100 mL of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to foscarnet and impurity B is at least 7.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Bacterial endotoxins

The endotoxin limit concentration is 2 IU per mL, Appendix XIV C.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a volume of the infusion with sufficient mobile phase to produce a solution containing 0.10% w/v of Foscarnet Sodium.

(2) 0.10% w/v of *foscarnet sodium BPCRS*.

(3) 0.02% w/v of *foscarnet sodium BPCRS* and 0.02% w/v of *foscarnet impurity B BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related esters may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuvienthuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to foscarnet and impurity B is at least 7.0.

DETERMINATION OF CONTENT

Calculate the content of $CNa_3O_5P,6H_2O$ in the infusion using the declared content of $CNa_3O_5P,6H_2O$ in *foscarnet sodium BPCRS*.

STORAGE

Foscarnet Infusion should be stored at a temperature not exceeding 30°. It should not be refrigerated.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C and D listed under Foscarnet Sodium.

© Crown Copyright 2022

www.webofpharma.com

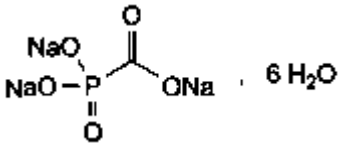
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Foscarnet Sodium

General Notices

(Foscarnet Sodium Hexahydrate, Ph. Eur. monograph 1520)



$CNa_3O_5P,6H_2O$ 300.0 *34156-56-4*

Action and use

Antiviral (cytomegalovirus).

Preparation

Foscarnet Infusion

Ph Eur

DEFINITION

Trisodium phosphonatoformate hexahydrate.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *foscarnet sodium hexahydrate CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is not more opalescent than reference suspension I (*2.2.1*) and is colourless (*2.2.2, Method II*).

pH (*2.2.3*)

9.0 to 11.0 for solution S.

Impurity D

Gas chromatography (*2.2.28*).

Test solution Dissolve 0.250 g of the substance to be examined in 9.0 mL of a 6 g/L solution of *glacial acetic acid R* using a magnetic stirrer. Add 1.0 mL of *anhydrous ethanol R* and mix.

Reference solution Dissolve 25.0 mg of *foscarnet impurity D CRS* in *anhydrous ethanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *anhydrous ethanol R*.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.31 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Split ratio 1:20.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 8	100 → 180
Injection port		200

www.webofpharma.com

https://thuocngocanh.com/

	Time (min)	Temperature (°C)
Detector		250

Detection Flame ionisation.

Injection 3 µL

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5 mg of *foscarnet impurity B CRS* in the mobile phase, add 2 mL of the test solution and dilute to 50 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *foscarnet impurity mixture CRS* (impurities A and C) in 1 mL of mobile phase.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase Dissolve 3.22 g of *sodium sulfate decahydrate R* in *water for chromatography R*, add 3 mL of *glacial acetic acid R* and 6 mL of a 44.61 g/L solution of *sodium pyrophosphate R* and dilute to 1000 mL with *water for chromatography R* (solution A); dissolve 3.22 g of *sodium sulfate decahydrate R* in *water for chromatography R*, add 6.8 g of *sodium acetate R* and 6 mL of a 44.61 g/L solution of *sodium pyrophosphate R* and dilute to 1000 mL with *water for chromatography R* (solution B). Mix about 700 mL of solution A and about 300 mL of solution B to obtain a solution of pH 4.4. To 1000 mL of this solution, add 0.25 g of *tetrahexylammonium hydrogen sulfate R* and 100 mL of *methanol R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 40 µL.

Run time 2.5 times the retention time of foscarnet.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *foscarnet impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and C; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention With reference to foscarnet (retention time = about 5 min): impurity A = about 0.7; impurity B = about 1.5; impurity C = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 7.0 between the peaks due to foscarnet and impurity B.

Limits:

— *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.04 per cent); disregard any peak with a relative retention less than 0.6.

Phosphate and phosphite

Liquid chromatography (*2.2.29*).

Test solution Dissolve 60.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 28 mg of *sodium dihydrogen phosphate monohydrate R* in *water R* and dilute to 100 mL with the same solvent.

Reference solution (b) Dissolve 43 mg of *sodium phosphite pentahydrate R* in *water R* and dilute to 100 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of reference solution (a) and 1.0 mL of reference solution (b) to 25 mL with *water R*.

Reference solution (d) Dilute 3 mL of reference solution (a) and 3 mL of reference solution (b) to 25 mL with *water R*.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

— *stationary phase*: *anion-exchange resin R*.

Mobile phase Dissolve 0.102 g of *potassium hydrogen phthalate R* in *water for chromatography R*, add 2.5 mL of *1 M nitric acid* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.4 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Spectrophotometer at 290 nm (indirect detection).

Injection 20 µL of the test solution and reference solutions (c) and (d).

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to phosphate (1st peak) and phosphite;

— *signal-to-noise ratio*: minimum 10 for the principal peak.

Limits:

— *phosphate*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *phosphite*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.3 per cent).

Loss on drying (*2.2.32*)

35.0 per cent to 37.0 per cent, determined on 1.000 g by drying in an oven at 150 °C.

Bacterial endotoxins (*2.6.14*)

Less than 83.3 IU/g, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 0.200 g in 50 mL of *water R*. Titrate with *0.05 M sulfuric acid*, determining the end-point potentiometrically (*2.2.20*) at the 1st point of inflexion.

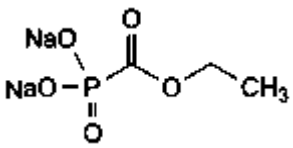
1 mL of *0.05 M sulfuric acid* is equivalent to 19.20 mg of CNa_3O_5P.

STORAGE

Protected from light.

IMPURITIES

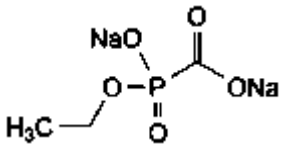
Specified impurities *A, B, C, D.*



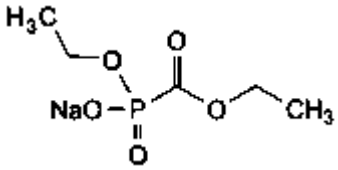
A. disodium (ethoxycarbonyl)phosphonate,

www.webofpharma.com

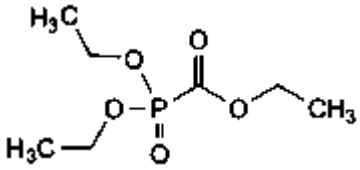
https://thuocngocanh.com/



B. disodium (ethoxyoxydophosphanyl)formate,



C. ethyl sodium (ethoxycarbonyl)phosphonate,



D. ethyl (diethoxyphosphoryl)formate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

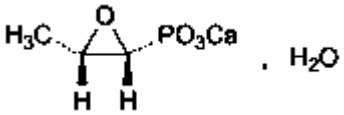
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fosfomycin Calcium

General Notices

(Ph. Eur. monograph 1328)



$C_3H_5CaO_4P,H_2O$ 194.1 *26469-67-0*

Action and use

Phosphonic acid derivative; antibacterial.

Ph Eur

DEFINITION

Calcium (2*R*,3*S*)-(3-methyloxiran-2-yl)phosphonate monohydrate.

Substance produced by certain strains of *Streptomyces fradiae* or obtained by any other means.

Content

95.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, practically insoluble in acetone, in methanol and in methylene chloride.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *fosfomycin calcium CRS*.

B. Dissolve about 0.1 g in 3 mL of a 25 per cent *V/V* solution of *perchloric acid R*. Add 1 mL of *0.1 M sodium periodate* and heat on a water-bath for 30 min. Allow to cool and add 50 mL of *water R*. Neutralise with a saturated solution of *sodium hydrogen carbonate R* and add 1 mL of a freshly prepared 400 g/L solution of *potassium iodide R*. Prepare a blank at the same time and in the same manner. The test solution remains colourless and the blank is orange.

C. To about 8 mg add 2 mL of *water R*, 1 mL of *perchloric acid R* and 2 mL of *0.1 M sodium periodate*. Heat on a water-bath for 10 min and add, without cooling, 1 mL of *ammonium molybdate solution R5* and 1 mL of *aminohydroxynaphthalenesulfonic acid solution R*. Allow to stand for 30 min. A blue colour develops.

D. It gives reaction (a) of calcium (*2.3.1*).

TESTS

pH (*2.2.3*)

8.1 to 9.6.

Dissolve 20 mg in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Specific optical rotation (*2.2.7*)

-11.0 to -13.0 (anhydrous substance), determined at 405 nm using a mercury lamp.

Dissolve 2.5 g in a 125 g/L solution of *sodium edetate R* previously adjusted to pH 8.5 with *strong sodium hydroxide solution R*, and dilute to 50.0 mL with the same solution.

Impurity A

Maximum 1.5 per cent.

In a glass-stoppered flask, dissolve 0.200 g in 100.0 mL of *water R*. Add 50 mL of 0.5 M phthalate buffer solution pH 6.4 R and 5.0 mL of *0.005 M sodium periodate*, close and shake. Allow to stand protected from light for 90 min. Add 10 mL of a freshly prepared 400 g/L solution of *potassium iodide R*, close and shake for 2 min. Titrate with *0.0025 M sodium arsenite* until the yellow colour almost disappears. Add 2 mL of *starch solution R* and slowly continue the titration until the colour is completely discharged. Carry out a blank test under the same conditions.

Calculate the percentage content of $C_3H_7CaO_5P$ using the following expression:

$$\frac{\left(n_1 - n_2\right) \times c \times 97 \times 100}{m\left(100 - H\right)} \times 100$$

m	=	mass of the substance to be examined, in milligrams;
n_1	=	volume of *0.0025 M sodium arsenite* used in the blank titration, in millilitres;
n_2	=	volume of *0.0025 M sodium arsenite* used in the titration of the test solution, in millilitres;

www.webofpharma.com

https://thuocngocanh.com/

c	=	molarity of the sodium arsenite solution;
H	=	percentage content of water.

Chlorides (2.4.4)

Maximum 0.2 per cent.

Dissolve 0.500 g in *water R*, add 2 mL of *nitric acid R* and dilute to 50 mL with the same acid. To 2.5 mL of this solution add 12.5 mL of *water R*.

Water (2.5.12)

8.5 per cent to 11.5 per cent, determined on 0.250 g. Use as the solvent a mixture of 1 volume of *pyridine R* and 3 volumes of *ethylene glycol R*.

ASSAY

In a glass-stoppered flask, dissolve 0.120 g in 20.0 mL of *0.1 M sodium periodate*. Add 5 mL of a 50 per cent *V/V* solution of *perchloric acid R* and shake. Heat in a water-bath at 37 °C for 105 min. Add 50 mL of *water R* and immediately adjust to pH 6.4 with a saturated solution of *sodium hydrogen carbonate R*. Add 10 mL of a freshly prepared 400 g/L solution of *potassium iodide R*, close and allow to stand for 2 min. Titrate with *0.1 M sodium arsenite* until the yellow colour almost disappears. Add 2 mL of *starch solution R* and slowly continue the titration until the colour is completely discharged. Carry out a blank test under the same conditions.

Calculate the percentage content of $C_3H_5CaO_4P$ using the following expression:

$$\frac{\left(n_1 - n_2\right) \times c \times 88 \times 100}{m\left(100 - H\right)} \times (100 - G)$$

m	=	mass of the substance to be examined, in milligrams;
n_1	=	volume of *0.1 M sodium arsenite* used in the blank titration, in millilitres;
n_2	=	volume of *0.1 M sodium arsenite* used in the titration of the test solution, in millilitres;
c	=	molarity of the sodium arsenite solution;
G	=	percentage content of impurity A;
H	=	percentage content of water.

STORAGE

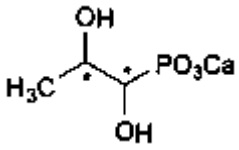
In an airtight container, protected from light.

IMPURITIES

Specified impurities A.

www.webofpharma.com

https://thuocngocanh.com/



A. calcium (1,2-dihydroxypropyl)phosphonate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

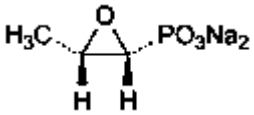
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fosfomycin Sodium

General Notices

(Ph. Eur. monograph 1329)



$C_3H_5Na_2O_4P$ 182.0 *26016-99-9*

Action and use

Phosphonic acid derivative; antibacterial.

Ph Eur

DEFINITION

Disodium (2*R*,3*S*)-(3-methyloxiran-2-yl)phosphonate.

Substance produced by certain strains of *Streptomyces fradiae* or obtained by any other means.

Content

95.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, very hygroscopic powder.

Solubility

Very soluble in water, sparingly soluble in methanol, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Preparation Discs of *potassium bromide R*.

Comparison *Ph. Eur. reference spectrum of fosfomycin sodium*.

B. Dissolve about 0.1 g in 3 mL of a 25 per cent *V/V* solution of *perchloric acid R*. Add 1 mL of *0.1 M sodium periodate* and heat on a water-bath for 30 min. Allow to cool and add 50 mL of *water R*. Neutralise with a saturated solution of *sodium hydrogen carbonate R* and add 1 mL of a freshly prepared 400 g/L solution of *potassium iodide R*. Prepare a blank at the same time and in the same manner. The test solution remains colourless and the blank is orange.

C. To about 8 mg add 2 mL of *water R*, 1 mL of *perchloric acid R* and 2 mL of *0.1 M sodium periodate*. Heat on a water-bath for 10 min and add, without cooling, 1 mL of *ammonium molybdate solution R5* and 1 mL of *aminohydroxynaphthalenesulfonic acid solution R*. Allow to stand for 30 min. A blue colour develops.

D. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution B_9 (*2.2.2, Method II*).

pH (*2.2.3*)

9.0 to 10.5.

Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*)

-13.0 to -15.0 (anhydrous substance), determined at 405 nm using a mercury lamp.

Dissolve 2.5 g in *water R* and dilute to 50.0 mL with the same solvent.

Impurity A

Maximum 1.0 per cent.

In a glass-stoppered flask, dissolve 0.200 g in 100.0 mL of *water R*. Add 50 mL of *0.5 M phthalate buffer solution pH 6.4 R* and 5.0 mL of *0.005 M sodium periodate*, close and shake. Allow to stand protected from light for 90 min. Add 10 mL of a freshly prepared 400 g/L solution of *potassium iodide R*, close and shake for 2 min. Titrate with *0.0025 M sodium arsenite* until the yellow colour almost disappears. Add 2 mL of *starch solution R* and slowly continue the titration until the colour is completely discharged. Carry out a blank test under the same conditions.

Calculate the percentage content of $C_3H_7Na_2O_5P$ using the following expression:

www.webofpharma.com

https://thuocngocanh.com/

$$\frac{(n_1 - n_2) \times c \times 100 \times 100}{m(100 - H)} \times 100$$

m	=	mass of the substance to be examined, in milligrams;
n_1	=	volume of *0.0025 M sodium arsenite* used in the blank titration, in millilitres;
n_2	=	volume of *0.0025 M sodium arsenite* used in the titration of the test solution, in millilitres;
c	=	molarity of the sodium arsenite solution;
H	=	percentage content of water.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.50 g. Use as the solvent a mixture of 1 volume of *pyridine R* and 3 volumes of *ethylene glycol R*.

Bacterial endotoxins (*2.6.14*)

Less than 0.083 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

In a glass-stoppered flask, dissolve 0.120 g in 20.0 mL of *0.1 M sodium periodate*. Add 5 mL of a 50 per cent *V/V* solution of *perchloric acid R* and shake. Heat in a water-bath at 37 °C for 105 min. Add 50 mL of *water R* and immediately adjust to pH 6.4 with a saturated solution of *sodium hydrogen carbonate R*. Add 10 mL of a freshly prepared 400 g/L solution of *potassium iodide R*, close and allow to stand for 2 min. Titrate with *0.1 M sodium arsenite* until the yellow colour almost disappears. Add 2 mL of *starch solution R* and slowly continue the titration until the colour is completely discharged. Carry out a blank test under the same conditions.

Calculate the percentage content of $C_3H_5Na_2O_4P$ using the following expression:

$$\frac{(n_1 - n_2) \times c \times 91 \times 100}{m(100 - H)} \times (100 - G)$$

m	=	mass of the substance to be examined, in milligrams;
n_1	=	volume of *0.1 M sodium arsenite* used in the blank titration, in millilitres;
n_2	=	volume of *0.1 M sodium arsenite* used in the titration of the test solution, in millilitres;
c	=	molarity of the sodium arsenite solution;
G	=	percentage content of impurity A;
H	=	percentage content of water.

STORAGE

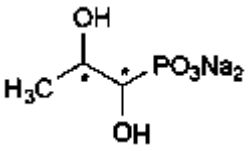
In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

Specified impurities *A.*



A. disodium (1,2-dihydroxypropyl)phosphonate.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

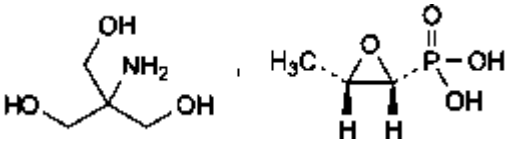
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fosfomycin Trometamol

General Notices

(Ph. Eur. monograph 1425)



$C_7H_{18}NO_7P$ 259.2 *78964-85-9*

Action and use

Phosphonic acid derivative; antibacterial.

Ph Eur

DEFINITION

2-Amino-2-(hydroxymethyl)propane-1,3-diol hydrogen (2*R*,3*S*)-(3-methyloxiran-2-yl)phosphonate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Very soluble in water, slightly soluble in ethanol (96 per cent) and in methanol, practically insoluble in acetone.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *fosfomycin trometamol CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 50 mg of *fosfomycin trometamol CRS* in *water R* and dilute to 10 mL with the same solvent.

Plate *cellulose for chromatography R* as the coating substance.

Mobile phase *concentrated ammonia R*, *water R*, *2-propanol R* (10:20:70 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In a current of warm air.

Detection Expose to iodine vapour until the spots appear.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. To about 15 mg add 2 mL of *water R*, 1 mL of *perchloric acid R* and 2 mL of *0.1 M sodium periodate*. Heat on a water-bath for 10 min and add, without cooling, 1 mL of *ammonium molybdate solution R5* and 1 mL of *aminohydroxynaphthalenesulfonic acid solution R*. Allow to stand for 30 min. A blue colour develops.

TESTS

Solution S

Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

pH (*2.2.3*)

3.5 to 5.5 for solution S.

Specific optical rotation (*2.2.7*)

-13.5 to -12.5 (anhydrous substance), determined on solution S at 365 nm using a mercury lamp.

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.600 g of the substance to be examined in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (a) Dissolve 0.600 g of *fosfomycin trometamol CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 3.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Wet 0.3 g of the substance to be examined with 60 µL of *water R* and heat in an oven at 60 °C for 24 h. Dissolve the residue in the mobile phase and dilute to 20.0 mL with the mobile phase (solution A). Dissolve 0.6 g of the substance to be examined in solution A and dilute to 5.0 mL with the same solution (*in situ* degradation to obtain impurities A, B, C and D).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm).

Mobile phase 10.89 g/L solution of *potassium dihydrogen phosphate R* in *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Differential refractometer at 35 °C.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of fosfomycin.

Relative retention With reference to fosfomycin (retention time = about 9 min): trometamol (2 peaks) = about 0.3; impurity B = about 0.48; impurity C = about 0.54; impurity A = about 0.88; impurity D = about 1.27.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity A and fosfomycin,

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Limits:

— *impurities A, B*: for each impurity, not more than the area of the peak due to fosfomycin in the chromatogram obtained with reference solution (b) (0.3 per cent),

— *impurities C, D*: for each impurity, not more than 0.33 times the area of the peak due to fosfomycin in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *unspecified impurities*: for each impurity, not more than 0.33 times the area of the peak due to fosfomycin in the chromatogram obtained with reference solution (b) (0.1 per cent),

— *total*: not more than 1.67 times the area of the peak due to fosfomycin in the chromatogram obtained with reference solution (b) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *disregard limit*: 0.17 times the area of the peak due to fosfomycin in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the 2 peaks due to trometamol.

Phosphates

Maximum 500 ppm.

Dissolve 0.1 g in 3 mL of *dilute nitric acid R* and dilute to 10 mL with *water R*. To 5 mL of this solution add 5 mL of *water R* and 5 mL of *molybdovanadic reagent R*. Shake vigorously. After 5 min, any colour in the test solution is not more intense than that in a standard prepared at the same time in the same manner, using 5 mL of *phosphate standard solution (5 ppm PO_4) R*.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 0.500 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 5 µL of the test solution and reference solution (a).

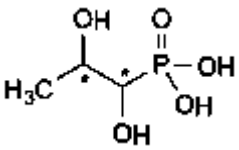
Calculate the percentage content of $C_7H_{18}NO_7P$ from the areas of the peaks due to fosfomycin and the declared content of *fosfomycin trometamol CRS*.

STORAGE

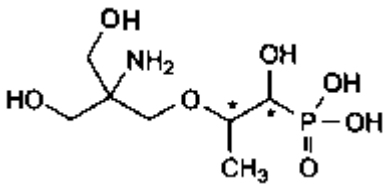
In an airtight container.

IMPURITIES

Specified impurities *A, B, C, D.*



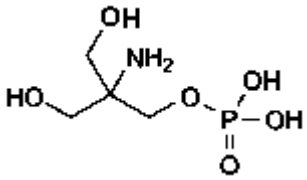
A. (1,2-dihydroxypropyl)phosphonic acid,



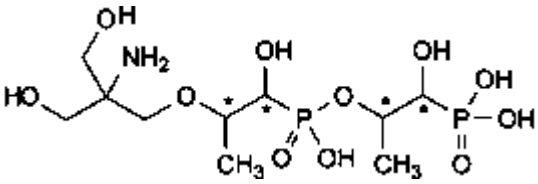
B. [2-[2-amino-3-hydroxy-2-(hydroxymethyl)propoxy]-1-hydroxypropyl]phosphonic acid,

www.webofpharma.com

https://thuocngocanh.com/



C. 2-amino-3-hydroxy-2-(hydroxymethyl)propyl dihydrogen phosphate (trometamol phosphoric acid monoester),



D. [2-[[[2-[2-amino-3-hydroxy-2-(hydroxymethyl)propoxy]-1-hydroxypropyl]hydroxyphosphoryl]oxy]-1-hydroxypropyl]phosphonic acid (trometamoyloxy fosfomycin dimer).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

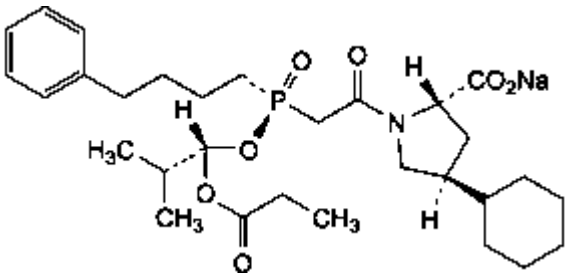
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fosinopril Sodium

General Notices

(Ph. Eur. monograph 1751)



$C_{30}H_{45}NNaO_7P$ 585.7 *88889-14-9*

Action and use

Angiotensin converting enzyme inhibitor.

Preparation

Fosinopril Tablets

Ph Eur

DEFINITION

Sodium (2*S*,4*S*)-4-cyclohexyl-1-[[(*R*)-[(1*S*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2-carboxylate.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in hexane.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Specific optical rotation (2.2.7): -6.7 to -4.7 (anhydrous substance).

Dissolve 0.500 g in *methanol R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *fosinopril sodium CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in a 2 per cent *V/V* solution of *water R* in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. It gives reaction (a) of sodium (2.3.1).

TESTS

Related substances

A. Liquid chromatography (2.2.29).

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Sonicate until dissolution is complete.

Reference solution (a) Dissolve 2 mg of the substance to be examined, 2 mg of *fosinopril impurity A CRS*, 2 mg of *fosinopril impurity B CRS*, 2 mg of *fosinopril impurity I CRS* and 2 mg of *fosinopril impurity K CRS* in the mobile phase and dilute to 50 mL with the mobile phase. Dilute 1 mL of the solution to 50 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dilute 5.0 mL of reference solution (b) to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: *silica gel for chromatography R* (5 µm);

— *temperature*: 33 °C.

Mobile phase *phosphoric acid R*, *water for chromatography R*, *acetonitrile R1* (0.05:0.35:100 *V/V/V*).

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

www.webofpharma.com

https://thuocngocanh.com/

Run time 4 times the retention time of fosinopril.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, I and K.

Relative retention With reference to fosinopril (retention time = about 5 min): impurity K = about 0.3; impurity I = about 0.5; impurities B, E and H = about 0.7; impurity A = about 2.0.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity B and fosinopril in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 40 for the principal peak in the chromatogram obtained with reference solution (c).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity I = 1.3; impurity K = 2.3;

— *sum of impurities B, E and H*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity K*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity I*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent).

B. Impurities C and D. Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase. Sonicate until dissolution is complete.

Reference solution (a) Dissolve 5.0 mg of the substance to be examined and 5.0 mg of *fosinopril impurity C CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Reference solution (c) Dissolve 5.0 mg of *fosinopril impurity D CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 10.0 mL of the solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *strong anion-exchange silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase *phosphoric acid R*, *water for chromatography R*, *acetonitrile R1* (0.2:1.5:400 *V/V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 20 µL.

Run time Twice the retention time of fosinopril.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to fosinopril (retention time = about 10 min): impurity C = about 1.2; impurity D = about 1.3.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to fosinopril and impurity C.

Limits:

— *impurity C*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent).

C. Impurities E and F. Liquid chromatography (*2.2.29*).

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 20.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *fosinopril impurity mixture CRS* (containing impurities E and F) in 1 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm);

www.webofpharma.com

https://thietbiuocngocanh.com/

— *temperature*: 45 °C.

Mobile phase 0.2 per cent *V/V* solution of *phosphoric acid R*, *acetonitrile R1* (44:56 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm.

Injection 20 µL of the test solution and reference solutions (b) and (c).

Run time 3 times the retention time of fosinopril.

Identification of impurities Use the chromatogram supplied with *fosinopril impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities E and F.

Relative retention With reference to fosinopril (retention time = about 8 min): impurity E = about 0.8; impurity F = about 0.9.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity F and fosinopril.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 0.7;

— *impurities E, F*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent).

2-Ethylhexanoic acid (2.4.28)

Maximum 0.2 per cent *m/m*.

Water (2.5.12)

Maximum 0.2 per cent, determined on 1.00 g.

ASSAY

Dissolve 0.400 g in 60 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 58.57 mg of $C_{30}H_{45}NNaO_7P$.

IMPURITIES

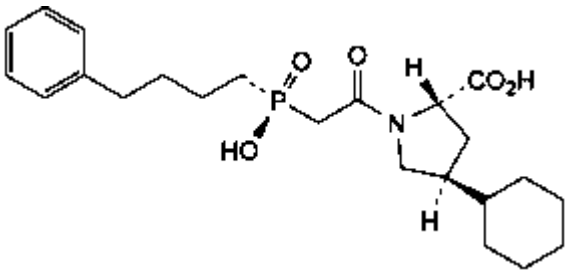
Specified impurities *A, B, C, D, E, F, H, I, K.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph

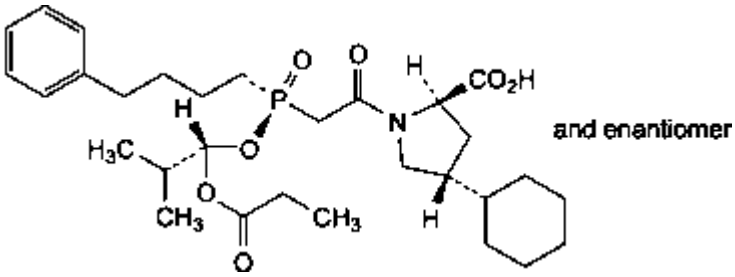
www.webofpharma.com

https://thuocngocanh.com/

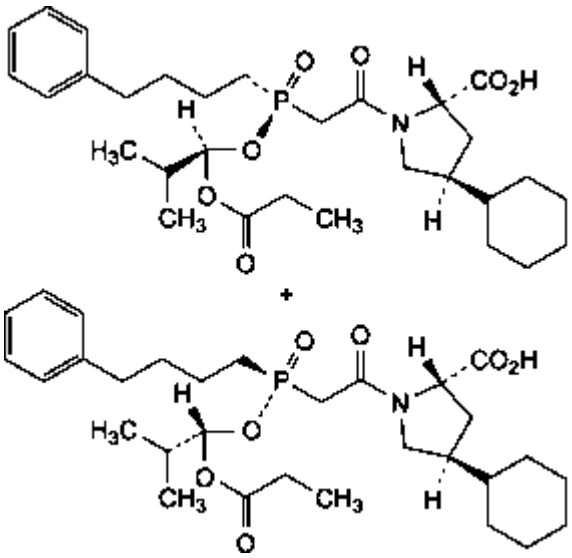
Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) N.



A. (2*S*,4*S*)-4-cyclohexyl-1-[[(*R*)-hydroxy(4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2-carboxylic acid,



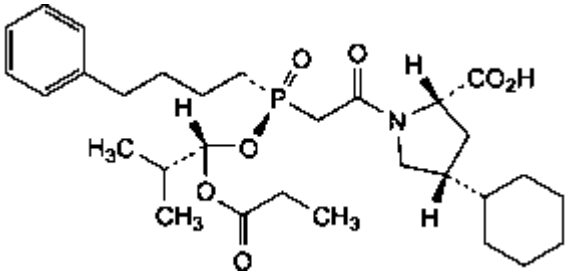
B. (2*RS*,4*RS*)-4-cyclohexyl-1-[[(*RS*)-[(1*SR*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2-carboxylic acid,



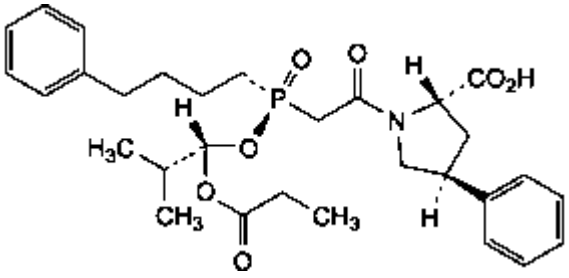
C. mixture of (2*S*,4*S*)-4-cyclohexyl-1-[[(*R*)-[(1*R*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2-carboxylic acid and (2*S*,4*S*)-4-cyclohexyl-1-[[(*S*)-[(1*S*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2-carboxylic acid,

www.webofpharma.com

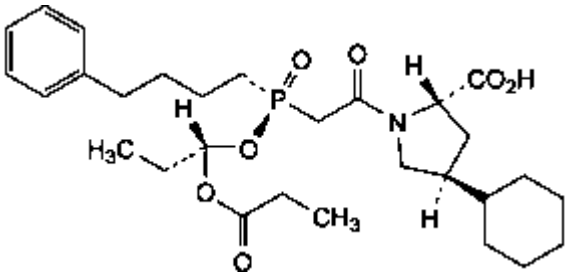
https://thuocngocanh.com/



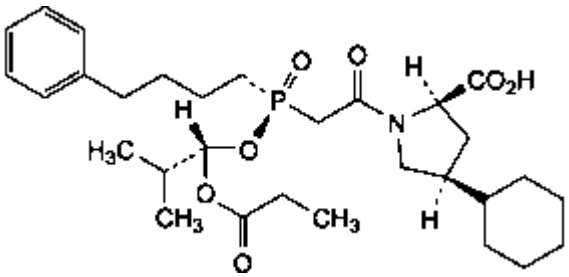
D. (2*S*,4*R*)-4-cyclohexyl-1-[[(*R*)-[(1*S*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2-carboxylic acid,



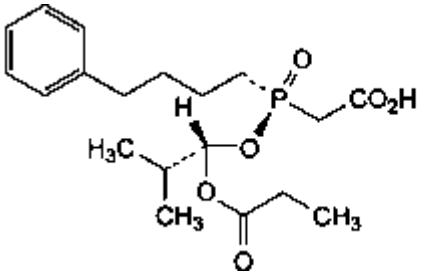
E. (2*S*,4*S*)-1-[[(*R*)-[(1*S*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetyl]-4-phenylpyrrolidine-2-carboxylic acid (phenylfosinopril),



F. (2*S*,4*S*)-4-cyclohexyl-1-[[(*R*)-(4-phenylbutyl)[(1*S*)-1-(propanoyloxy)propoxy]phosphoryl]acetyl]pyrrolidine-2-carboxylic acid,



H. (2*R*,4*S*)-4-cyclohexyl-1-[[(*R*)-[(1*S*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2-carboxylic acid,

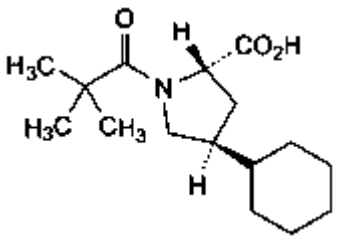


and enantiomer

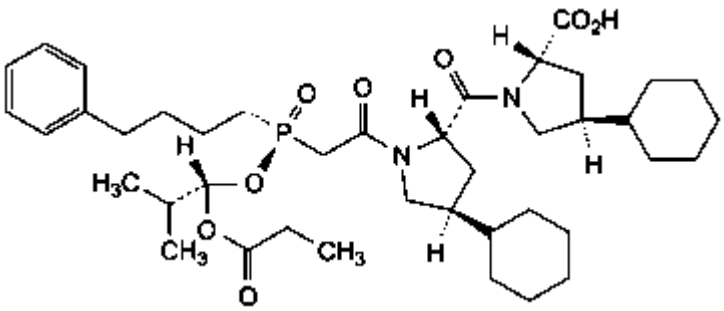
www.webofpharma.com

https://thuocngocanh.com/

I. [(*RS*)-[(1*SR*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetic acid,



K. (2*S*,4*S*)-4-cyclohexyl-1-(2,2-dimethylpropanoyloxy)pyrrolidine-2-carboxylic acid,



N. (2*S*,4*S*)-4-cyclohexyl-1-[(2*S*,4*S*)-4-cyclohexyl-1-[[(*R*)-[(1*S*)-2-methyl-1-(propanoyloxy)propoxy](4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2carbonyl]pyrrolidine-2-carboxylic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fosinopril Tablets

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Fosinopril Tablets contain Fosinopril Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of fosinopril sodium, $C_{30}H_{45}NNaO_7P$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 50 mg of Fosinopril Sodium with 40 mL of *water* and filter. Centrifuge, adjust the pH of the supernatant to 3.0 with *orthophosphoric acid* and filter. Wash the filter with several quantities of *dichloromethane*, collect the washings and evaporate to dryness under a stream of air and dry the residue for 10 minutes at 60° under vacuum. The infrared absorption spectrum, Appendix II A, of the oily residue is concordant with the *reference spectrum* of fosinopril sodium *(RS 472)*.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes withdraw a sample of the medium and filter. Use the filtered dissolution medium, diluted with *water* if necessary, to produce a solution expected to contain 0.0005% w/v of Fosinopril Sodium.

www.webofpharma.com

https://thuocngocanh.com/

(2) To 20 mg of *fosinopril sodium BPCRS* add 6 mL of *methanol*, dissolve with the aid of ultrasound and dilute to 100 mL with *water*. Dilute 1 volume of this solution to 40 volumes with *water*.

(3) 0.002% w/v each of *fosinopril sodium BPCRS* and *2-[hydroxyl(4-phenylbutyl)phosphinyl]-acetic acid BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm)(Waters Nova-Pak is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 3 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 215 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

36 volumes of a 0.2% w/v solution of *orthophosphoric acid* and 64 volumes of *acetonitrile R1*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fosinopril and 2-[hydroxyl(4-phenylbutyl)phosphinyl]-acetic acid is at least 1.7.

DETERMINATION OF CONTENT

Calculate the total content of fosinopril sodium, $C_{30}H_{45}NNaO_7P$, in the medium from the chromatograms obtained and using the declared content of $C_{30}H_{45}NNaO_7P$, in *fosinopril sodium BPCRS*.

LIMITS

The amount of fosinopril sodium released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile R1* and 80 volumes of 0.2M *urea* (solvent A).

(1) Dissolve a quantity of the powdered tablets containing 25 mg of Fosinopril Sodium with sufficient solvent A to produce a solution containing 0.05% w/v of Fosinopril Sodium.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.007% w/v of *fosinopril sodium BPCRS* and 0.003% w/v of *fosinopril impurity A BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Bondclone C18 or Hypersil ODS C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

www.webofpharma.com

https://thuocngocanh.com/

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 215 nm.

(f) Inject 50 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of fosinopril.

MOBILE PHASE

22 volumes of 0.2% v/v solution of *orthophosphoric acid* and 78 volumes of *methanol R1*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to fosinopril (retention time, about 7.6 minutes) of impurity A is about 0.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fosinopril and fosinopril impurity A is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity A (using solution (3)) and multiply the area of this peak by a correction factor of 0.8;

the area of any peak corresponding to fosinopril impurity A is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (5.0%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* excluding fosinopril impurity A is not greater than the area of principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 20 volumes of *acetonitrile R1* and 80 volumes of 0.2M *urea* (solvent B).

(1) To a quantity of the powdered tablets containing 50 mg of Fosinopril Sodium add 400 mL of solvent B, mix and add sufficient solvent B to produce 500 mL. Centrifuge an aliquot of the solution and use the supernatant liquid.

(2) 0.01% w/v of *fosinopril sodium BPCRS*.

(3) 0.007% w/v of *fosinoprol sodium BPCRS* and 0.003% w/v of *fosinopril impurity A BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to fosinopril and fosinopril impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{30}H_{45}NNaO_7P$ in the tablets using the declared content of $C_{30}H_{45}NNaO_7P$ in *fosinopril sodium BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Fosinopril Sodium.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fractionated Palm Kernel Oil

General Notices

The standards of this monograph encompass several different suppository bases. The selection of a basis for a particular suppository formulation should be appropriate to the product concerned and it may be necessary to apply more restrictive standards for a particular application.

Action and use

Suppository basis.

DEFINITION

Fractionated Palm Kernel Oil is obtained by expression of the natural oil from the kernels of *Elaeis guineensis* Jacq. followed by selective solvent fractionation and hydrogenation.

CHARACTERISTICS

A white, solid, brittle fat; odourless or almost odourless.

Practically insoluble in water; miscible with ether and with petroleum spirit (boiling range, 40° to 60°); practically insoluble in ethanol (96%).

TESTS

Acid value

Not more than 0.2, Appendix X B.

Iodine value

Not more than 6.0 *(iodine bromide method)*, Appendix X E.

Melting point

31° to 36°, Appendix V A, Method IV. Prepare the substance being examined in the following manner. Melt about 30 g in an oven at a temperature of 55° to 60° and filter through a suitable dry filter paper, maintaining the temperature between 53° and 60°. Cool with occasional stirring until the temperature falls to between 32° and 34°, stir continuously with a mechanical stirrer until the first signs of cloudiness appear and continue to stir by hand until the substance has the consistence of a paste. Immediately transfer to a vessel previously kept at a temperature of 15° to 22° and allow to stand at this temperature for 24 hours before carrying out the test.

Refractive index

At 50°, 1.445 to 1.447, Appendix V E.

www.webofpharma.com

https://thuocngocanh.com/

Saponification value

246 to 250, Appendix X G.

Peroxides

Dissolve 5 g in 15 mL of *chloroform*, add 20 mL of *glacial acetic acid* and 0.5 mL of a saturated solution of *potassium iodide*, mix well, allow to stand in the dark for exactly 1 minute, add 30 mL of *water* and titrate with 0.01M *sodium thiosulfate VS* using *starch mucilage* as indicator. Not more than 0.5 mL of 0.01M *sodium thiosulfate VS* is required.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

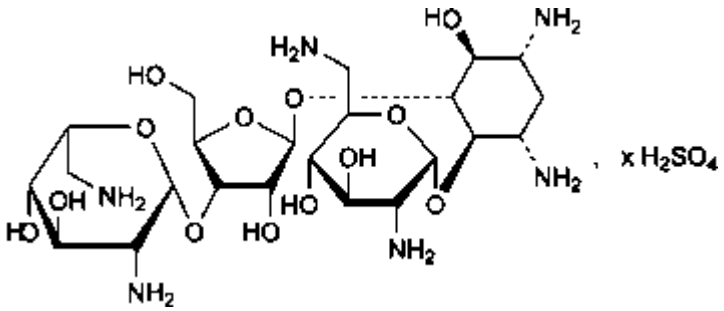
This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Framycetin Sulfate

General Notices

Framycetin Sulphate

(Ph. Eur. monograph 0180)



$C_{23}H_{46}N_6O_{13},xH_2SO_4$ 615 (base) *4146-30-9*

Action and use

Antibacterial.

Ph Eur

DEFINITION

Sulfate of 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-D-streptamine (neomycin B).

Substance produced by the growth of selected strains of *Streptomyces fradiae* or *Streptomyces decaris* or obtained by any other means.

Content

Minimum of 630 IU/mg (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder, hygroscopic.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

IDENTIFICATION

A. Examine the chromatograms obtained in the test for related substances.

Results:

— the retention time of the principal peak in the chromatogram obtained with the test solution is approximately the same as that of the principal peak in the chromatogram obtained with reference solution (a),

— it complies with the limit given for impurity C.

B. It gives reaction (a) of sulfates (*2.3.1*).

TESTS

pH (*2.2.3*)

6.0 to 7.0.

Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*)

+ 52.5 to + 55.5 (dried substance).

Dissolve 1.00 g in *water R* and dilute to 10.0 mL with the same solvent

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve the contents of a vial of *framycetin sulfate CRS* in the mobile phase and dilute with the mobile phase to obtain a solution containing 0.5 mg/mL.

Reference solution (b) Dilute 3.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve the contents of a vial of *neamine CRS* (corresponding to 0.5 mg) in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (e) Dissolve 10 mg of *neomycin sulfate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

www.webofpharma.com

https://thuocngocanh.com/

— *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 25 °C.

Mobile phase Mix 20.0 mL of *trifluoroacetic acid R*, 6.0 mL of *carbonate-free sodium hydroxide solution R* and 500 mL of *water R*, allow to equilibrate, dilute to 1000 mL with *water R* and degas.

Flow rate 0.7 mL/min.

Post-column solution *carbonate-free sodium hydroxide solution R* diluted 1 in 25 previously degassed, which is added pulse-less to the column effluent using a 375 µL polymeric mixing coil.

Flow rate 0.5 mL/min.

Detection Pulsed amperometric detector with a gold working electrode, a silver-silver chloride reference electrode and a stainless steel auxiliary electrode which is the cell body, held at respectively 0.00 V detection, + 0.80 V oxidation and -0.60 V reduction potentials, with pulse durations according to the instrument used.

Injection 10 µL.

Run time 1.5 times the retention time of neomycin B.

Relative retention With reference to neomycin B (retention time = about 10 min): impurity A = about 0.65; impurity C = about 0.9; impurity G = about 1.1.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to impurity C and to neomycin B in the chromatogram obtained with reference solution (e); if necessary, adjust the volume of the carbonate-free sodium hydroxide solution in the mobile phase,

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (c).

Limits:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) and taking into account the declared content of *neamine CRS* (1.0 per cent),

— *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent),

— *total of other impurities*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent),

— *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent).

Sulfate

27.0 per cent to 31.0 per cent (dried substance).

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.250 g in 100 mL of *water R* and adjust the solution to pH 11 using *concentrated ammonia R*. Add 10.0 mL of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate* adding 50 mL of *alcohol R* when the colour of the solution begins to change and continuing the titration until the violet-blue colour disappears.

1 mL of *0.1 M barium chloride* is equivalent to 9.606 mg of SO_4.

Loss on drying (*2.2.32*)

Maximum 8.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.7 kPa for 3 h.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 1.0 g.

Sterility (*2.6.1*)

If intended for introduction into body cavities without a further appropriate sterilisation procedure, it complies with the test for sterility.

Bacterial endotoxins (*2.6.14, Method D*)

Less than 1.3 IU/mg if intended for introduction into body cavities without a further appropriate procedure for the removal of bacterial endotoxins.

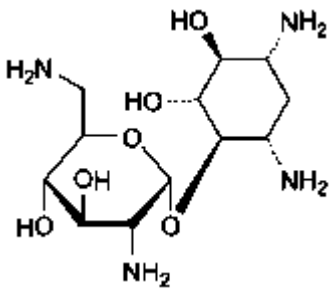
ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *framycetin sulfate CRS* as the reference substance.

STORAGE

In an airtight container, protected from light. If the substance is intended for introduction into body cavities, store in a sterile, tamper-evident container.

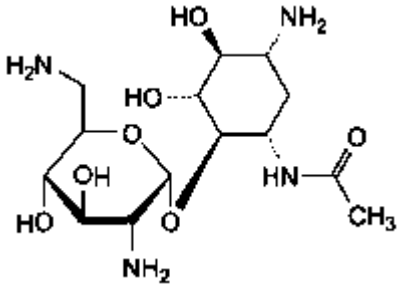
IMPURITIES



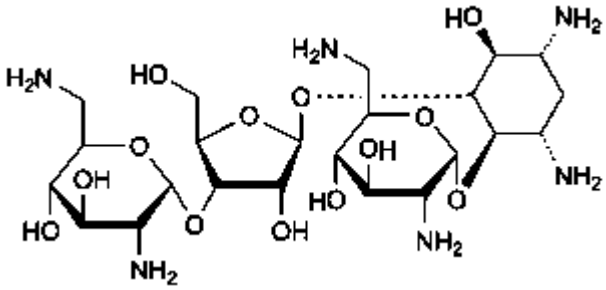
A. 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine (neamine or neomycin A-LP),

www.webofpharma.com

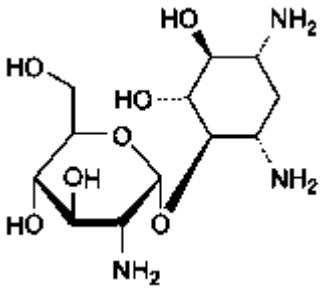
https://thuocngocanh.com/



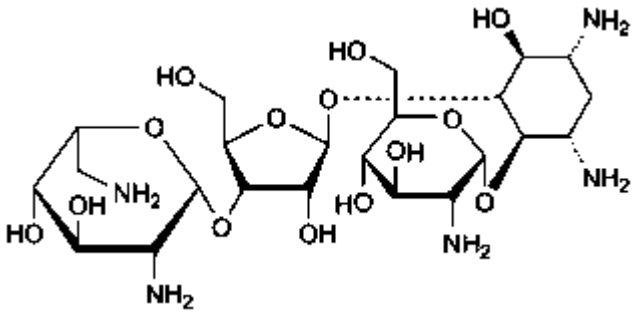
B. 3-*N*-acetyl-2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine (3-acetylneamine),



C. 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-β-D-ribofuranosyl]-D-streptamine (neomycin C),



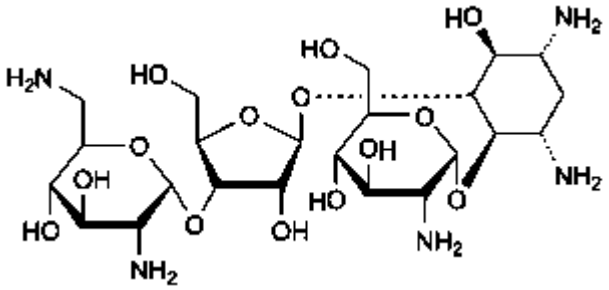
D. 4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-2-deoxy-D-streptamine (paromamine or neomycin D),



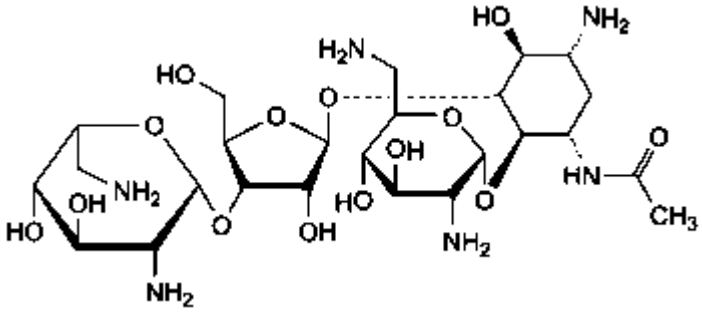
E. 4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-2-deoxy-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-D-streptamine (paromomycin I or neomycin E),

www.webofpharma.com

https://thuvienthuocngocanh.com/



F. 4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-2-deoxy-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-β-D-ribofuranosyl]-D-streptamine (paromomycin II or neomycin F),



G. 3-*N*-acetyl-2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-D-streptamine (neomycin B-LP).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

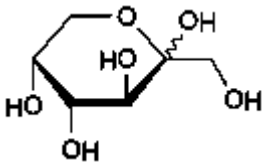
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Fructose

General Notices

(Ph. Eur. monograph 0188)



$C_6H_{12}O_6$ 180.2 *57-48-7*

Ph Eur

DEFINITION

D-*arabino*-Hex-2-ulopyranose (levulose).

The substance described in this monograph is not necessarily suitable for parenteral administration.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Solvent mixture water R, methanol R (40:60 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution Dissolve 10 mg of fructose CRS in the solvent mixture and dilute to 20 mL with the solvent mixture.

Plate TLC silica gel plate R.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase *water R*, *methanol R*, *anhydrous acetic acid R*, *methylene chloride R* (10:15:25:50 *V/V/V/V*). Measure the volumes accurately since a slight excess of water produces cloudiness.

Application 2 µL; thoroughly dry the points of application.

Development A Over 3/4 of the plate.

Drying A In a current of warm air.

Development B Immediately, over 3/4 of the plate, after renewing the mobile phase.

Drying B In a current of warm air.

Detection Spray with a solution of 0.5 g of *thymol R* in a mixture of 5 mL of *sulfuric acid R* and 95 mL of *ethanol (96 per cent) R*; heat at 130 °C for 10 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Dissolve 0.1 g in 10 mL of *water R*. Add 3 mL of *cupri-tartaric solution R* and heat. A red precipitate is formed.

C. To 1 mL of solution S (see Tests) add 9 mL of *water R*. To 1 mL of this solution add 5 mL of *hydrochloric acid R* and heat to 70 °C. A brown colour develops.

D. Dissolve 5 g in *water R* and dilute to 10 mL with the same solvent. To 0.5 mL of the solution add 0.2 g of *resorcinol R* and 9 mL of *dilute hydrochloric acid R* and heat on a water-bath for 2 min. A red colour develops.

TESTS

Solution S

Dissolve 10.0 g in *distilled water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Dissolve 5.0 g in *water R* and dilute to 10 mL with the same solvent. The solution is clear (*2.2.1*). Add 10 mL of *water R*. The solution is colourless (*2.2.2, Method II*).

Acidity or alkalinity

Dissolve 6.0 g in 25 mL of *carbon dioxide-free water R* and add 0.3 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.15 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Specific optical rotation (*2.2.7*)

-93.5 to -91.0 (anhydrous substance).

Dissolve 10.0 g in 80 mL of *water R*, add 0.2 mL of *dilute ammonia R1*, allow to stand for 30 min and dilute to 100.0 mL with *water R*.

Foreign sugars

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 5.0 g in *water R* and dilute to 10 mL with the same solvent. To 1 mL of the solution add 9 mL of *ethanol (96 per cent) R*. Any opalescence in the solution is not more intense than that in a mixture of 1 mL of the initial solution and 9 mL of *water R*.

5-Hydroxymethylfurfural and related compounds

To 5 mL of solution S add 5 mL of *water R*. The absorbance (*2.2.25*) of the solution determined at 284 nm is not greater than 0.32.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash

Maximum 0.1 per cent.

Dissolve 5.0 g in 10 mL of *water R*, add 2 mL of *sulfuric acid R*, evaporate to dryness on a water-bath and ignite to constant mass.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

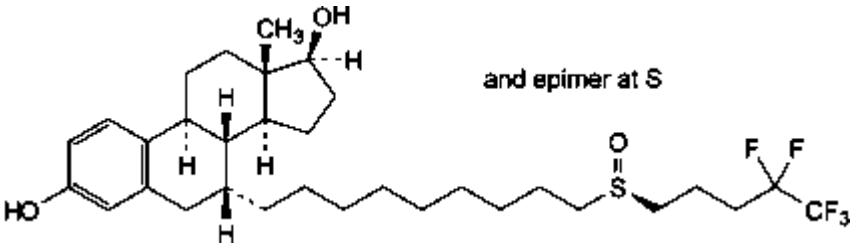
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Fulvestrant

General Notices

(Ph. Eur. monograph 2443)



$C_{32}H_{47}F_5O_3S$ 607 *129453-61-8*

Action and use

Oestrogen receptor antagonist.

Preparation

Fulvestrant Injection

Ph Eur

DEFINITION

7α-[9-[(*RS*)-4,4,5,5,5-Pentafluoropentane-1-sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent) and in methylene chloride.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Specific optical rotation (2.2.7): + 108 to + 115 (anhydrous substance), measured at 365 nm at a temperature of 25 °C.
Dissolve 0.50 g in *methanol R* and dilute to 25.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *fulvestrant CRS*.

C. Stereochemical purity (see Tests).

TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 0.1 g in *ethanol (96 per cent) R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in *methanol R1* and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dissolve 50.0 mg of *fulvestrant CRS* in *methanol R1* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *fulvestrant for system suitability CRS* (containing impurities A, B, C, D and F) in 1.0 mL of *methanol R1*.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R1*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R1*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *methanol R2*, *acetonitrile R1*, *water for chromatography R* (27:32:41 *V/V/V*);

— *mobile phase B*: *water for chromatography R*, *methanol R2*, *acetonitrile R1* (10:41:49 *V/V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 55	100 → 0	0 → 100
55 - 65	0	100

Flow rate 2 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *fulvestrant for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D and F.

Relative retention With reference to fulvestrant (retention time = about 23 min): impurity F = about 0.4; impurity A = about 1.1; impurity B = about 1.2; impurity C = about 1.7; impurity D = about 1.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to fulvestrant and impurity A.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 0.7; impurity F = 0.3;

— for each impurity, use the concentration of fulvestrant in reference solution (c).

Limits:

— *impurity D*: maximum 0.6 per cent;

— *impurity C*: maximum 0.3 per cent;

— *impurity B*: maximum 0.2 per cent;

— *impurity F*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Stereochemical purity

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution Dissolve 5 mg of *fulvestrant CRS* in the mobile phase and dilute to 5 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *amylose derivative of silica gel for chiral separation R* (5 µm);

— *temperature*: 25 °C.

Mobile phase *propanol R1*, *heptane R* (15:85 *V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL.

Run time Twice the retention time of fulvestrant epimer B.

Identification of peaks Use the chromatogram supplied with *fulvestrant CRS* and the chromatogram obtained with the reference solution to identify the peaks due to fulvestrant epimers A and B.

Relative retention With reference to fulvestrant epimer B (retention time = about 18 min): fulvestrant epimer A = about 1.2.

System suitability Reference solution:

— *resolution*: minimum 2.0 between the peaks due to fulvestrant epimer B and fulvestrant epimer A.

Limit:

— *fulvestrant epimer A*: 42 per cent to 48 per cent;

— *fulvestrant epimer B*: 52 per cent to 58 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 50 mg.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

Bacterial endotoxins (*2.6.14*)

www.webofpharma.com

https://thuocngocanh.com/

Less than 1.25 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

Test solution Dissolve 0.1 g of the substance to be examined in 1 mL of *ethanol (96 per cent) R* and dilute to 80 mL with water for BET.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{32}H_{47}F_5O_3S$ taking into account the assigned content of *fulvestrant CRS*.

STORAGE

Protected from light at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

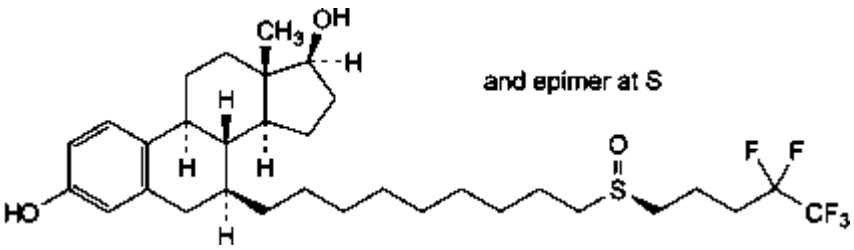
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

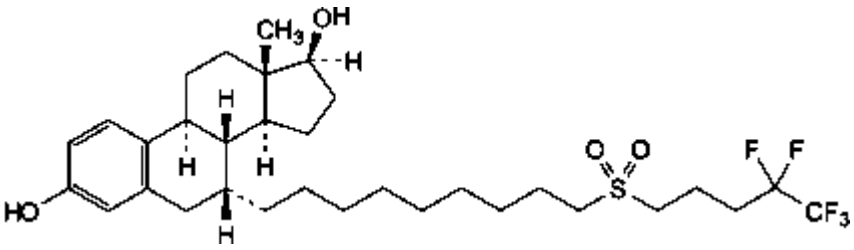
IMPURITIES

Specified impurities *B, C, D, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, E.*



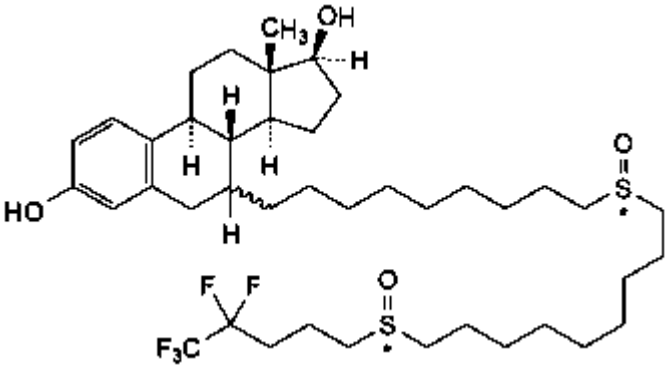
A. 7β-[9-[(*RS*)-4,4,5,5,5-pentafluoropentane-1-sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol (7β-fulvestrant),



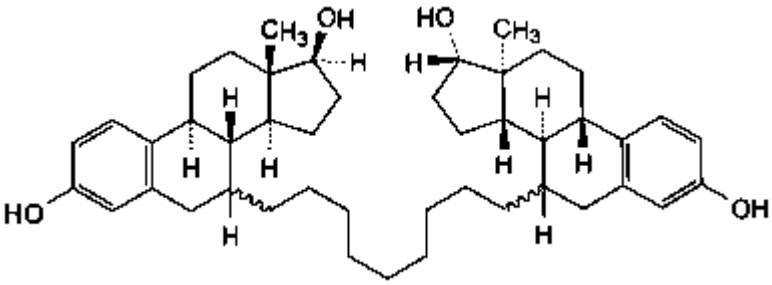
www.webofpharma.com

https://thuocngocanh.com/

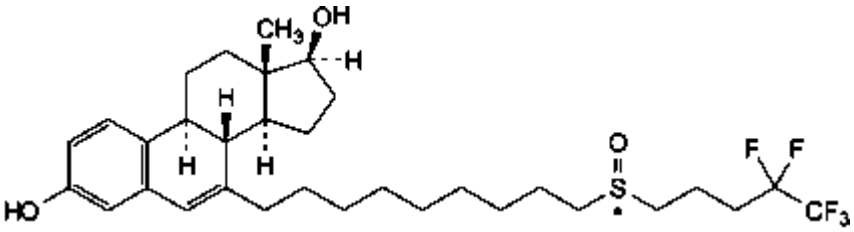
B. 7α-[9-(4,4,5,5,5-pentafluoropentane-1-sulfonyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol,



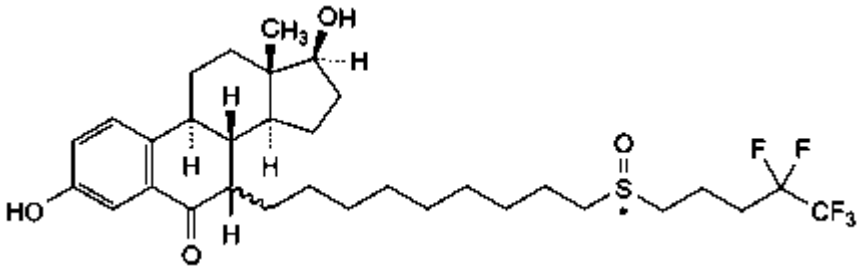
C. 7ξ-[9-[(Ξ)-9-[(Ξ)-4,4,5,5,5-pentafluoropentane-1-sulfinyl]nonane-1-sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol,



D. 7ξ,7′ξ-nonane-1,9-diyldi(estra-1,3,5(10)-triene-3,17β-diol),



E. 7-[9-[(Ξ)-4,4,5,5,5-pentafluoropentane-1-sulfinyl]nonyl]estra-1,3,5(10),6-tetraene-3,17β-diol (Δ6-fulvestrant),



F. 3,17β-dihydroxy-7ξ-[9-[(Ξ)-4,4,5,5,5-pentafluoropentane-1-sulfinyl]nonyl]estra-1,3,5(10)-trien-6-one (6-keto-fulvestrant).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Fulvestrant Injection

General Notices

(Ph. Eur. monograph 3096)

Action and use

Oestrogen receptor antagonist.

Ph Eur

DEFINITION

Sterile solution for injection of *Fulvestrant (2443)*, for human use.

It complies with the monograph Parenteral preparations (0520) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of fulvestrant ($C_{32}H_{47}F_5O_3S$) stated on the label.

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

C. Infrared absorption spectrophotometry (*2.2.24*).

Solvent mixture *ether R*, *2-methylpentane R* (35:65 *V/V*).

www.webofpharma.com

https://thuocngocanh.com/

Preconditioning Condition a silica solid phase extraction (SPE) cartridge with 10 mL of the solvent mixture at a flow rate of about 5 mL/min.

Test solution Dilute the contents of the preparation to be examined with the solvent mixture to obtain a concentration of fulvestrant of 10 mg/mL. With minimal delay, as fulvestrant may precipitate out of solution, load 1 mL of this solution onto the SPE cartridge at a flow rate of about 1 mL/min. Wash first with 10 mL of the solvent mixture at a flow rate of about 5 mL/min and then with 10 mL of *ether R* at a flow rate of about 1 mL/min to remove most of the excipients. Discard the washings. Elute with 10 mL of *ether R* at a flow rate of about 1 mL/min. The volumes used for washing and elution may be adjusted. Usually, 5 to 15 mL is sufficient to wash the cartridge and 10 to 20 mL is used for the elution. Collect the eluate and evaporate to about 0.5 mL under a stream of *nitrogen R* (fulvestrant may precipitate out of the solution). This is the test solution.

Preparation of the disc If recording in transmission mode, apply successive aliquots of the test solution (including any precipitated fulvestrant) to a disc of *potassium bromide R* allowing the solvent to evaporate before each addition. Repeat until all of the test solution has been applied to the disc. Allow to stand for 5 min, crush and prepare a new disc.

Comparison *fulvestrant CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dilute a volume of the preparation to be examined containing the equivalent of 50 mg of fulvestrant in 5.0 mL of *methanol R*.

Reference solution (a) Dissolve 50.0 mg of *fulvestrant CRS* in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *fulvestrant for system suitability CRS* (containing impurities A, B, C and D) in 1 mL of *methanol R*.

Reference solution (c) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *methanol R1*, *acetonitrile for chromatography R*, *water for chromatography R* (27:32:41 *V/V/V*);

— *mobile phase B*: *water for chromatography R*, *methanol R1*, *acetonitrile for chromatography R* (10:41:49 *V/V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 55	100 → 0	0 → 100
55 - 65	0	100

Flow rate 2 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram supplied with *fulvestrant for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to fulvestrant (retention time = about 22 min): impurity A = about 1.1; impurity B = about 1.2; impurity C = about 1.6; impurity D = about 1.8.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to fulvestrant and impurity A.

Calculation of percentage contents:

— for each impurity, use the concentration of fulvestrant in reference solution (c).

Limits:

— *impurity B*: maximum 1.0 per cent;

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 1.2 per cent;

— *reporting threshold*: 0.1 per cent; disregard the peaks due to impurities C and D.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the percentage content of fulvestrant ($C_{32}H_{47}F_5O_3S$) taking into account the assigned content of *fulvestrant CRS*.

www.webofpharma.com

https://thuocngocanh.com/

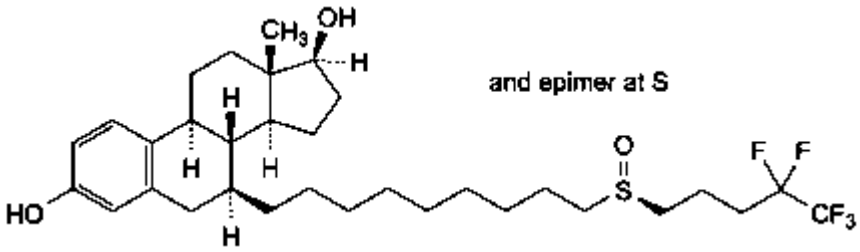
STORAGE

In a sterile, airtight, tamper-evident container, protected from light at a temperature of 2 °C to 8 °C.

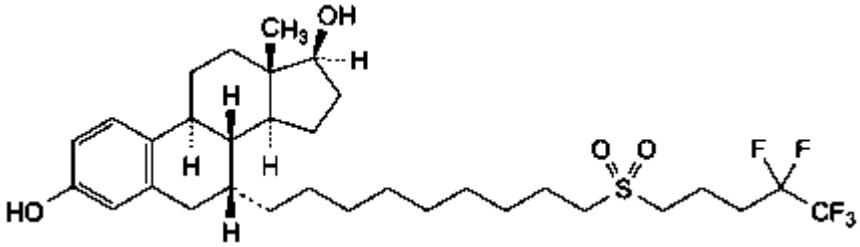
IMPURITIES

Specified impurities *B*.

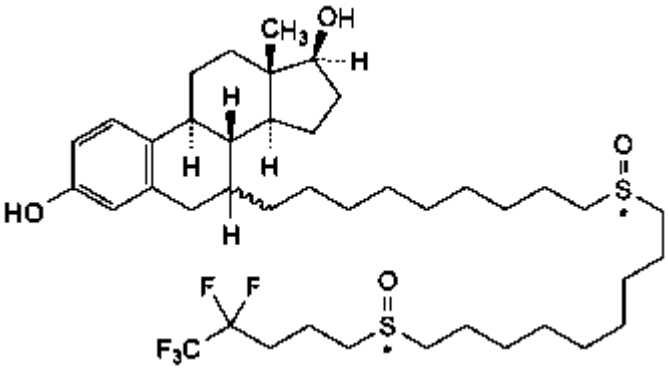
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, C, D, E, F*.



A. 7β-[9-[(*RS*)-4,4,5,5,5-pentafluoropentane-1-sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol (7β-fulvestrant),



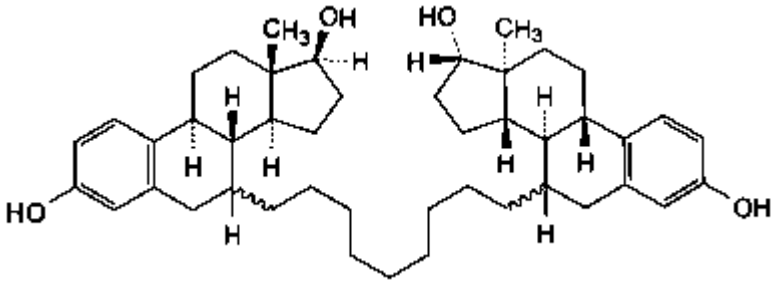
B. 7α-[9-(4,4,5,5,5-pentafluoropentane-1-sulfonyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol,



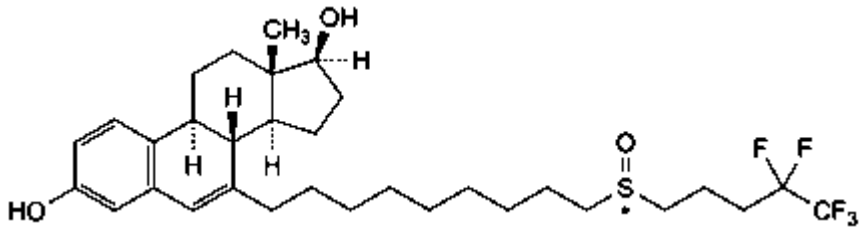
C. 7ξ-[9-[(Ξ)-9-[(Ξ)-4,4,5,5,5-pentafluoropentane-1-sulfinyl]nonane-1-sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol,

www.webofpharma.com

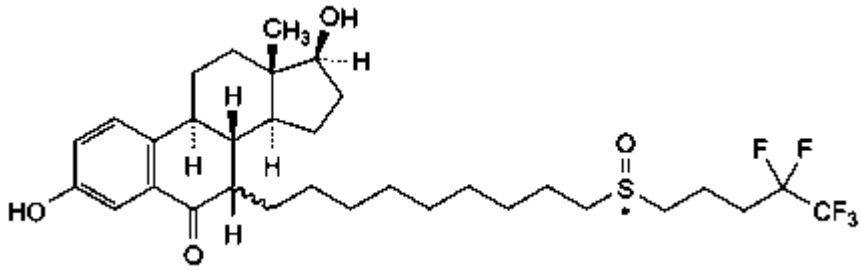
https://thuocngocanh.com/



D. 7ξ,7′ξ-nonane-1,9-diyldi(estra-1,3,5(10)-triene-3,17β-diol),



E. 7-[9-[(Ξ)-4,4,5,5,5-pentafluoropentane-1-sulfinyl]nonyl]estra-1,3,5(10),6-tetraene-3,17β-diol (Δ6-fulvestrant),



F. 3,17β-dihydroxy-7ξ-[9-[(Ξ)-4,4,5,5,5-pentafluoropentane-1-sulfinyl]nonyl]estra-1,3,5(10)-trien-6-one (6-keto-fulvestrant).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

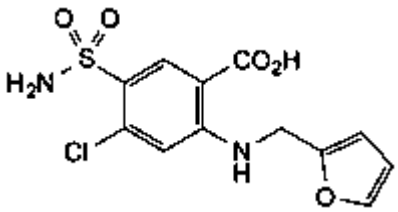
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Furosemide

General Notices

(Ph. Eur. monograph 0391)



$C_{12}H_{11}ClN_2O_5S$ 330.7 *54-31-9*

Action and use

Loop diuretic.

Preparations

Co-amilofruse Tablets

Furosemide Injection

Furosemide Oral Solution

Furosemide Tablets

Ph Eur

DEFINITION

4-Chloro-2-[[(furan-2-yl)methyl]amino]-5-sulfamoylbenzoic acid.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (5.9).

IDENTIFICATION

First identification: B.

Second identification: A.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in 1 mL of *methanol R*.

Reference solution Dissolve 20 mg of *furosemide CRS* in 1 mL of *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *glacial acetic acid R*, *ethyl acetate R*, *toluene R* (5:45:50 *V/V/V*).

Application 2 µL; the volume may be adapted according to the type of plate used.

Development Over 2/3 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

Detection B Treat with *ninhydrin solution R*, dry at 100-105 °C until the spots appear and examine in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *furosemide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_5 (2.2.2, *Method II*).

www.webofpharma.com

https://thuocngocanh.com/

Dissolve 0.5 g in *0.5 M sodium hydroxide* and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use and protect from light*.

Test solution Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 2 mg of *furosemide impurity A CRS* in the mobile phase, add 2.0 mL of the test solution and dilute to 20.0 mL with the mobile phase. Dilute 0.5 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 2 mg of *furosemide for peak identification CRS* (containing impurities C and D) in 2.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 2.0 g of *potassium dihydrogen phosphate R* and 2.5 g of *cetrimide R* in 700 mL of *water for chromatography R*, adjust to pH 7.0 with *ammonia R* and add 300 mL of *propanol R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 238 nm.

Injection 20 µL.

Run time 3 times the retention time of furosemide.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *furosemide for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C and D.

Relative retention With reference to furosemide (retention time = about 9 min): impurity C = about 0.5; impurity A = about 0.8; impurity D = about 1.5.

System suitability:

— *resolution*: minimum 4.0 between the peaks due to impurity A and furosemide in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 40 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.4; impurity D = 2.0;

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chlorides (*2.4.4*)

Maximum 200 ppm.

To 0.5 g add a mixture of 0.2 mL of *nitric acid R* and 30 mL of *water R* and shake for 5 min. Allow to stand for 15 min and filter.

Sulfates (*2.4.13*)

Maximum 300 ppm.

To 1.0 g add a mixture of 0.2 mL of *acetic acid R* and 30 mL of *distilled water R* and shake for 5 min. Allow to stand for 15 min and filter.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 40 mL of *dimethylformamide R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 33.07 mg of $C_{12}H_{11}ClN_2O_5S$.

STORAGE

Protected from light.

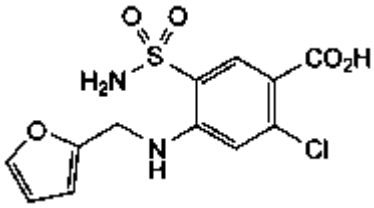
IMPURITIES

www.webofpharma.com

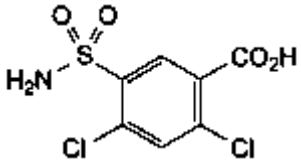
https://thuocngocanh.com/

Specified impurities C, D.

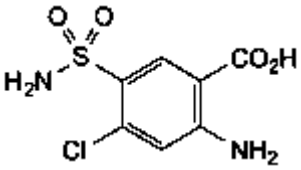
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, E, F.



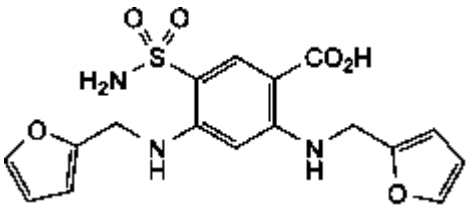
A. 2-chloro-4-[[(furan-2-yl)methyl]amino]-5-sulfamoylbenzoic acid,



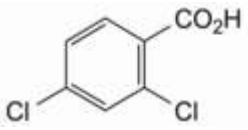
B. 2,4-dichloro-5-sulfamoylbenzoic acid,



C. 2-amino-4-chloro-5-sulfamoylbenzoic acid,



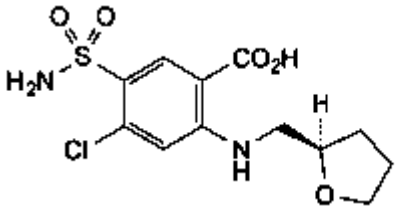
D. 2,4-bis[[(furan-2-yl)methyl]amino]-5-sulfamoylbenzoic acid,



E. 2,4-dichlorobenzoic acid,

www.webofpharma.com

https://thuocngocanh.com/



and enantiomer

F. 4-chloro-5-sulfamoyl-2-[[[(2*RS*)-oxolan-2-yl]methyl]amino]benzoic acid.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Furosemide Injection

General Notices

Furosemide Infusion

Action and use

Loop diuretic.

DEFINITION

Furosemide Injection is a sterile solution of furosemide sodium, prepared by the interaction of Furosemide with Sodium Hydroxide, in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of furosemide, $C_{12}H_{11}ClN_2O_5S$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless or almost colourless solution.

IDENTIFICATION

A. To a volume containing the equivalent of 20 mg of Furosemide add sufficient *water* to produce 100 mL. Dilute 5 mL to 100 mL with 0.1M *sodium hydroxide*. The *light absorption*, Appendix II B, in the range 220 to 320 nm exhibits two maxima, at 228 nm and 271 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH, 8.0 to 9.3, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase. Prepare the solutions immediately before use and protect from light.

(1) Dilute a volume of the injection to produce a solution containing 0.1% w/v of Furosemide.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.00025% w/v of each of *furosemide BPCRS* and *furosemide impurity A EPCRS*.

(4) 0.1% w/v of *furosemide for peak identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Symmetry C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 100 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of furosemide.

MOBILE PHASE

0.286% w/v of *potassium dihydrogen phosphate* and 0.357% w/v of *cetrimide* in *water*, adjusted to pH 7.0 using 6M *ammonia* (solution A).

30 volumes of *propan-1-ol* and 70 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to furosemide (retention time about 9 minutes) are: impurity C, about 0.5; impurity A, about 0.8 and impurity D, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and furosemide is at least 4.0.

LIMITS

Identify any peak due to impurity C and impurity D using solution (4) and multiply the area of the peak by a correction factor of 1.4 and 2 respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity D is not greater than 1.5 times area of the principal peak in the chromatogram obtained with solution (5) (0.15%);

the area of any other *secondary peak* is not greater than 1.3 times the area of the principal peak in the chromatogram obtained with solution (5) (0.13%);

the sum of the areas of any *secondary peaks* excluding impurity C is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%).

www.webofpharma.com

https://thietbiduocngocanh.com/

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection with *water BET*, if necessary, to contain the equivalent of 10 mg of furosemide per mL (solution A). The endotoxin limit concentration of this solution is 35 IU of endotoxin per mL.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase. Prepare the solutions immediately before use and protect from light.

(1) Dilute a quantity of the injection to produce a solution containing 0.01% w/v of Furosemide.

(2) 0.01% w/v of *furosemide BPCRS*.

(3) 0.00025% w/v each of *furosemide BPCRS* and *furosemide impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to impurity A and furosemide is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of furosemide, $C_{12}H_{11}ClN_2O_5S$, in the injection from the chromatograms obtained and using the declared content of $C_{12}H_{11}ClN_2O_5S$ in *furosemide BPCRS*.

STORAGE

Furosemide Injection should be protected from light.

LABELLING

The strength is stated in terms of the equivalent amount of furosemide in a suitable dose-volume.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Furosemide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Furosemide Oral Solution

General Notices

Action and use

Loop diuretic

DEFINITION

Furosemide Oral Solution is a solution of Furosemide in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of furosemide, $C_{12}H_{11}ClN_2O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a quantity of the oral solution with *methanol*, if necessary, to produce a solution containing 0.033% w/v of Furosemide.

(2) 0.033% w/v of *furosemide BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck TLC Si 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 5 cm.

(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *acetic acid*, 45 volumes of *ethyl acetate* and 50 volumes of *toluene*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity or alkalinity

pH, 7.0 to 9.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase. Prepare the solutions immediately before use and protect from light.

(1) Dilute a quantity of the oral solution containing 20 mg of Furosemide to 50 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.00025% w/v of each of *furosemide BPCRS* and *furosemide impurity A EPCRS*.

(4) 0.04% w/v of *furosemide for peak identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Luna C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 100 µL of each solution.

(g) Allow the chromatography to proceed for three times the retention time of furosemide.

MOBILE PHASE

0.286% w/v of *potassium dihydrogen phosphate* and 0.357% w/v of *cetrimide* in *water*, adjusted to pH 7.0 using 6M *ammonia* (solution A).

30 volumes of *propan-1-ol* and 70 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to furosemide (retention time about 9 minutes) are: impurity C, about 0.5; impurity A, about 0.8 and impurity D, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and furosemide is at least 4.0.

LIMITS

Identify any peak due to impurity C and impurity D using solution (4) and multiply the area of the peak by a correction factor of 1.4 and 2 respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peaks corresponding to impurity A, B or D is not greater than half the area of the peak in the chromatogram obtained with solution (2) (0.25%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) To a weighed quantity of the oral solution containing 20 mg of Furosemide, add 20 mL of 1M *sodium hydroxide* and dilute to 100 mL with the mobile phase. Further dilute 1 volume of this solution to 5 volumes.
(2) 0.004% w/v of *furosemide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 228 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile* and 70 volumes of a solution of 0.012% w/v of *sodium dihydrogen orthophosphate*, previously adjusted to pH 4.2 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of furosemide is about 3 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *symmetry factor* of the peak due to furosemide is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{12}H_{11}ClN_2O_5S$, weight in volume, using the declared content of $C_{12}H_{11}ClN_2O_5S$ in *furosemide BPCRS*.

STORAGE

www.webofpharma.com

https://thuathuocngocanh.com/

Furosemide Oral Solution should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Furosemide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Furosemide Tablets

General Notices

Action and use

Loop diuretic.

DEFINITION

Furosemide Tablets contain Furosemide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of furosemide, $C_{12}H_{11}ClN_2O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.2 g of Furosemide with 300 mL of 0.1M *sodium hydroxide* for 10 minutes, add sufficient 0.1M *sodium hydroxide* to produce 500 mL and filter. Dilute 5 mL to 250 mL with 0.1M *sodium hydroxide*. The *light absorption*, Appendix II B in the range 220 to 320 nm exhibits two maxima, at 228 nm and 271 nm.

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Tablets containing less than 100 mg of Furosemide comply with the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 5.8*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, to produce a solution expected to contain 0.001% w/v of Furosemide at the maximum at 277 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.001% w/v solution of *furosemide BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of furosemide, $C_{12}H_{11}ClN_2O_5S$, in the medium from the absorbances obtained and using the declared content of $C_{12}H_{11}ClN_2O_5S$ in *furosemide BPCRS*.

LIMITS

The amount of furosemide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase. Prepare the solutions immediately before use and protect from light.

(1) Shake a quantity of the powdered tablets containing 20 mg of Furosemide in sufficient mobile phase to produce 50 mL and mix with the aid of ultrasound for 15 minutes.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.00008% w/v of each of *furosemide BPCRS* and *furosemide impurity A EPCRS*.
(4) 0.04% w/v of *furosemide for peak identification EPCRS*.
(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Symmetry C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 238 nm.
(f) Inject 100 µL of each solution.
(g) Allow the chromatography to proceed for three times the retention time of furosemide.

MOBILE PHASE

0.286% w/v of *potassium dihydrogen phosphate* and 0.357% w/v of *cetrimide* in *water*, adjusted to pH 7.0 using 6M *ammonia* (solution A).

30 volumes of *propan-1-ol* and 70 volumes of solution A.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to furosemide (retention time about 9 minutes) are: impurity C, about 0.5; impurity A, about 0.8 and impurity D, about 1.5.

SYSTEM SUITABILITY

Identify any peak due to impurity C and impurity D using solution (4) and multiply the area of the peak by a correction factor of 1.4 and 2 respectively.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and furosemide is at least 4.0.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

The area of any peak corresponding to impurity C is not greater than 1.6 times the area of the peak in the chromatogram obtained with solution (2) (0.8%);

the area of any peak corresponding to impurity D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared in the mobile phase. Prepare the solutions immediately before use and protect from light.

(1) Shake a quantity of the powdered tablets containing 20 mg of Furosemide in sufficient mobile phase to produce 20 mL, mix with the aid of ultrasound for 15 minutes and filter. Dilute 1 volume of the filtrate to 10 volumes.
(2) 0.01% w/v of *furosemide BPCRS*.
(3) 0.00025% w/v each of *furosemide BPCRS* and *furosemide impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions stated under Related substances may be used, using an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless the *resolution* between the peaks due to impurity A and furosemide is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of furosemide, $C_{12}H_{11}ClN_2O_5S$, in the tablets from the chromatograms obtained and using the declared content of $C_{12}H_{11}ClN_2O_5S$ in *furosemide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Furosemide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

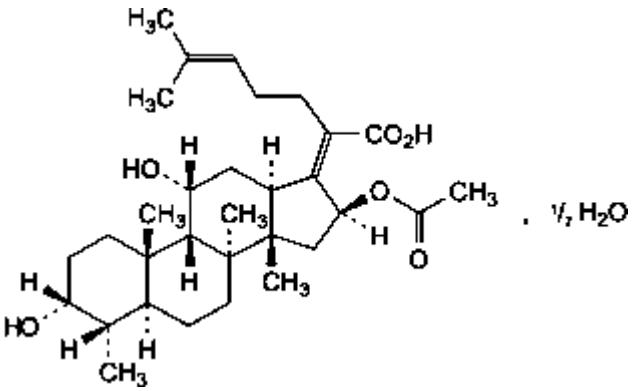
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fusidic Acid

General Notices

(Ph. Eur. monograph 0798)



$C_{31}H_{48}O_6,½H_2O$ 525.7 *6990-06-3*

Action and use

Antibacterial.

Preparations

Fusidic Acid Cream

Fusidic Acid Eye Drops

Fusidic Acid Oral Suspension

Ph Eur

DEFINITION

ent-(17*Z*)-16α-(Acetyloxy)-3β,11β-dihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid hemihydrate.

Antimicrobial substance produced by fermentation of certain strains of *Fusidium coccineum* or by any other means.

Content

97.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

www.webofpharma.com

https://thuocngocanh.com/

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *fusidic acid CRS*.

B. Ignite 1 g. The residue does not give reaction (a) of sodium (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solvent mixture *methanol R*, 5 g/L solution of *phosphoric acid R*, *acetonitrile R* (10:40:50 *V/V/V*).

Test solution Dissolve 25 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of *fusidic acid for peak identification CRS* (containing impurities A, B, C, D, F, G, H and N) in the solvent mixture and dilute to 1.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve the contents of a vial of *fusidic acid impurity mixture CRS* (containing impurities I, K, L and M) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, *acetonitrile R*, 5 g/L solution of *phosphoric acid R* (20:40:40 *V/V/V*);

— *mobile phase B*: 5 g/L solution of *phosphoric acid R*, *methanol R*, *acetonitrile R* (10:20:70 *V/V/V*);

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 28	100 → 0	0 → 100
28 - 33	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *fusidic acid for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, F, G, H and N; use the chromatogram supplied with *fusidic acid impurity mixture CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities I, K, L and M.

Relative retention With reference to fusidic acid (retention time = about 18 min): impurity A = about 0.4; impurity B = about 0.5; impurity C = about 0.6; impurity D = about 0.63; impurity N = about 0.65; impurity F = about 0.7; impurity G = about 0.82; impurity H = about 0.85; impurity I = about 0.96; impurity K = about 1.18; impurity L = about 1.23; impurity M = about 1.4.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to impurities G and H.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.7; impurity D = 0.7; impurity F = 0.3; impurity I = 0.6; impurity K = 0.6;

— *impurity M*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *impurity G*: not more than 0.7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);

— *impurity L*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *impurity B*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.4 per cent);

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities C, D, F, I, K, N*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (2.5.12)

1.4 per cent to 2.0 per cent, determined on 0.50 g.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 10 mL of *ethanol (96 per cent) R*. Add 0.5 mL of *phenolphthalein solution R*. Titrate with *0.1 M sodium hydroxide* until a pink colour is obtained.

1 mL of *0.1 M sodium hydroxide* is equivalent to 51.67 mg of $C_{31}H_{48}O_6$.

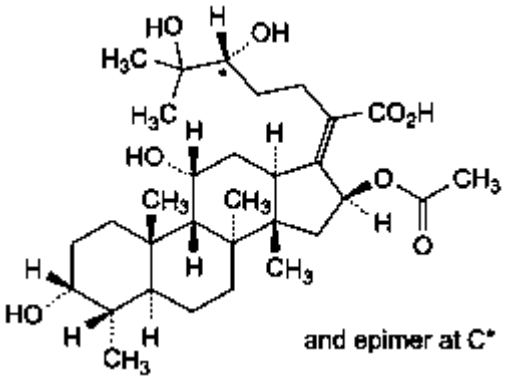
STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities A, B, C, D, F, G, I, K, L, M, N.

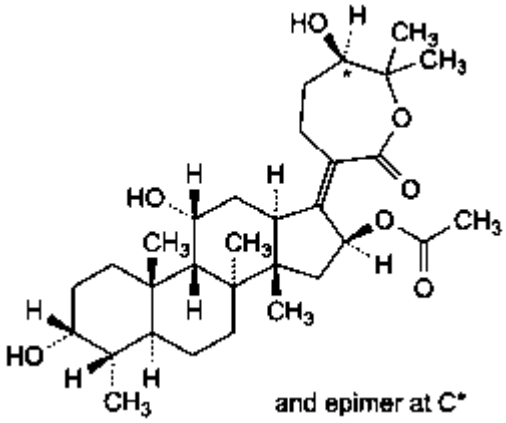
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) E, H, J, O.



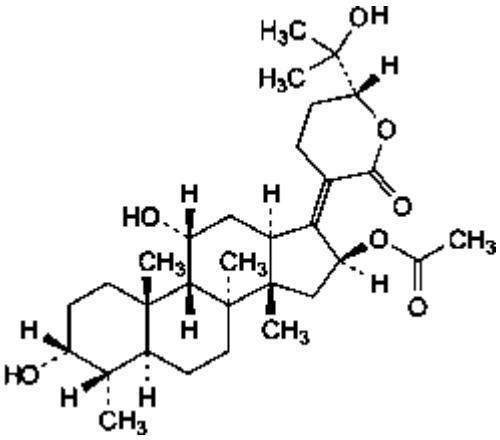
www.webofpharma.com

https://thuocngocanh.com/

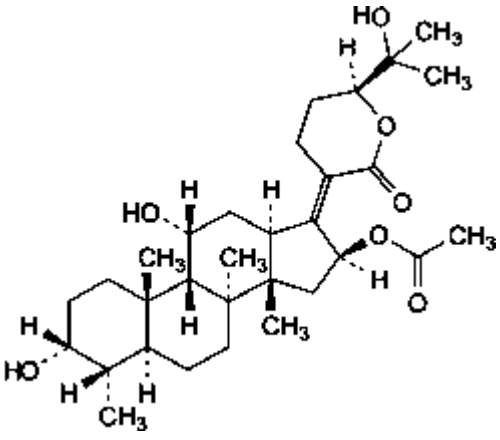
A. *ent*-(24*SR*,17*Z*)-16α-(acetyloxy)-3β,11β,24,25-tetrahydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholest-17(20)-en-21-oic acid (24,25-dihydro-24,25-dihydroxyfusidic acid),



B. *ent*-(17*Z*)-3β,11β-dihydroxy-17-[(6*SR*)-6-hydroxy-7,7-dimethyl-2-oxooxepan-3-ylidene]-4β,8,14-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate (24,25-dihydro-24,25-dihydroxyfusidic acid 21,25-lactone),



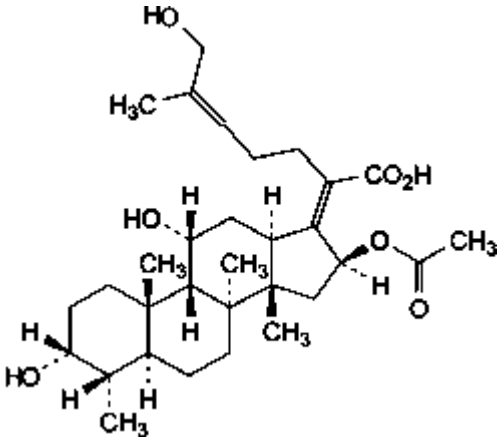
C. *ent*-(17*Z*)-3β,11β-dihydroxy-17-[(6*S*)-6-(1-hydroxy-1-methylethyl)-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene]-4β,8,14-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate ((24*R*)-24,25-dihydro-24,25-dihydroxyfusidic acid 21,24-lactone),



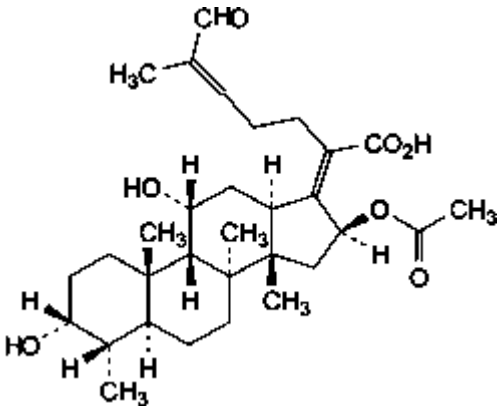
D. *ent*-(17*Z*)-3β,11β-dihydroxy-17-[(6*R*)-6-(1-hydroxy-1-methylethyl)-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene]-4β,8,14-trimethyl-18-nor-5β,10α-androstan-16α-yl acetate ((24*S*)-24,25-dihydro-24,25-dihydroxyfusidic acid 21,24-lactone),

www.webofpharma.com

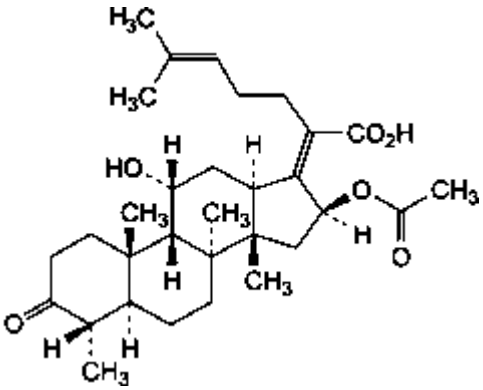
https://thuocngocanh.com/



E. *ent*-(17*Z*,24*EZ*)-16α-(acetyloxy)-3β,11β,26-trihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (26-hydroxyfusidic acid),



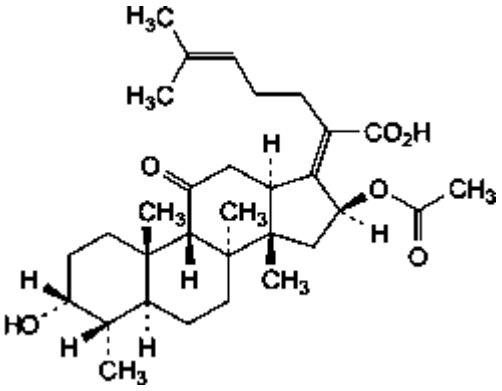
F. *ent*-(17*Z*,24*EZ*)-16α-(acetyloxy)-3β,11β-dihydroxy-4β,8,14-trimethyl-26-oxo-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (26-oxofusidic acid),



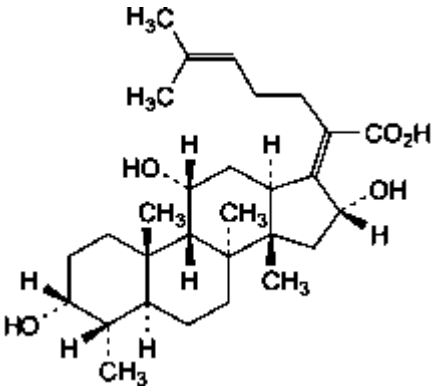
G. *ent*-(17*Z*)-16α-(acetyloxy)-11β-hydroxy-4β,8,14-trimethyl-3-oxo-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (3-didehydrofusidic acid),

www.webofpharma.com

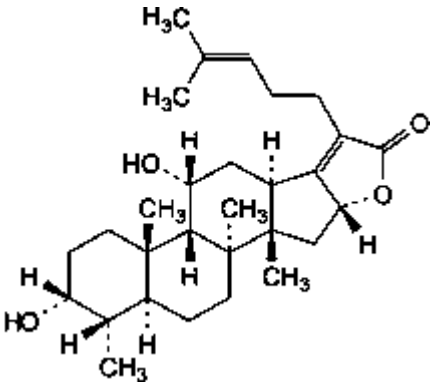
https://thuvienthuocngocanh.com/



H. *ent*-(17*Z*)-16α-(acetyloxy)-3β-hydroxy-4β,8,14-trimethyl-11-oxo-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (11-didehydrofusidic acid),



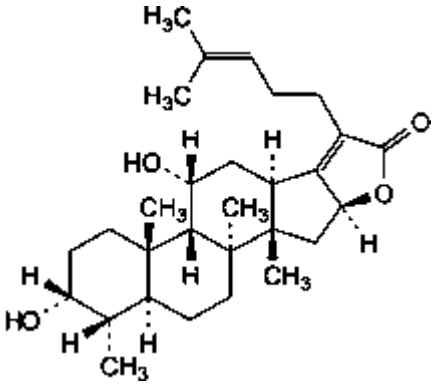
I. *ent*-(17*Z*)-3β,11β,16β-trihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (16-*epi*-deacetylfusidic acid),



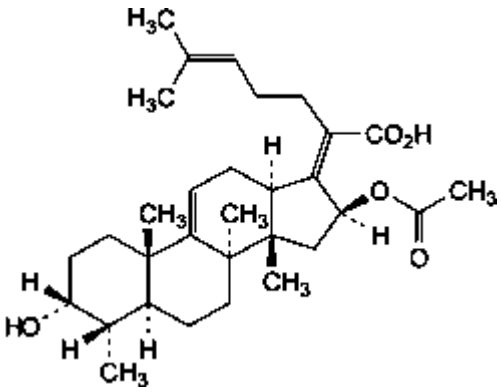
J. *ent*-(17*Z*)-3β,11β-dihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dieno-21(16β)-lactone (16-*epi*-deacetylfusidic acid 21,16-lactone),

www.webofpharma.com

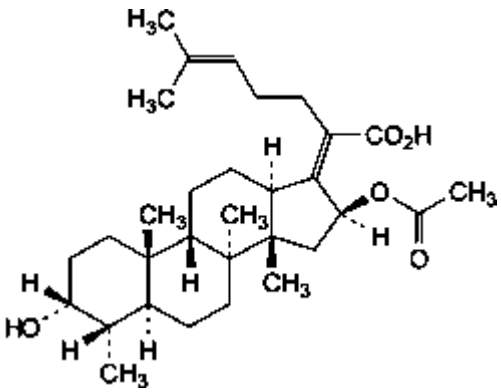
https://thuocngocanh.com/



K. *ent*-(17*Z*)-3β,11β-dihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dieno-21(16α)-lactone (deacetylfusidic acid 21,16-lactone),



L. *ent*-(17*Z*)-16α-(acetyloxy)-3β-hydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-9(11),17(20),24-trien-21-oic acid (9,11-anhydrofusidic acid),

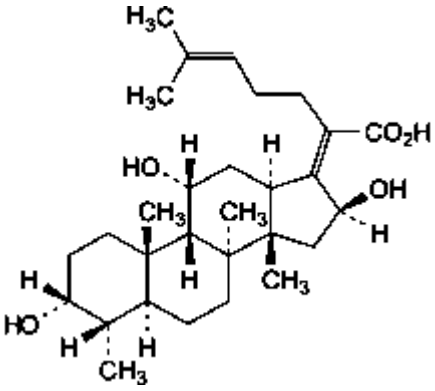


M. *ent*-(17*Z*)-16α-(acetyloxy)-3β-hydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (11-deoxyfusidic acid),

N. unknown structure,

www.webofpharma.com

https://thuocngocanh.com/



O. *ent*-(17*Z*)-3β,11β,16α-trihydroxy-4β,8,14-trimethyl-18-nor-5β,10α-cholesta-17(20),24-dien-21-oic acid (deacetylfusidic acid).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fusidic Acid Cream

General Notices

Action and use

Antibacterial.

DEFINITION

Fusidic Acid Cream contains Fusidic Acid in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of anhydrous fusidic acid, $C_{31}H_{48}O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse, with shaking, a quantity of the cream containing the equivalent of 40 mg of anhydrous fusidic acid in 10 mL of *ethanol (96%)*, filter and use the filtrate.

(2) 0.5% w/v of *diethanolamine fusidate BPCRS* in *ethanol (96%)*.

(3) 0.05% w/v of *potassium sorbate* and 0.5% w/v of *diethanolamine fusidate BPCRS* in *ethanol (96%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254} plate* (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12.5 cm.

(e) After removal of the plate, dry in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2.5 volumes of *methanol*, 10 volumes of *glacial acetic acid*, 10 volumes of *cyclohexane* and 80 volumes of *dichloromethane*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to fusidic acid in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 4.0 to 6.0, determined directly on the cream, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in Solution A.

Solution A 10 volumes of *methanol*, 40 volumes of 0.05M *orthophosphoric acid* and 50 volumes of *acetonitrile*.

(1) Disperse a quantity of the cream containing the equivalent of 25 mg of anhydrous fusidic acid in 8 mL of solution A, heat until the cream has dispersed and shake vigorously for 15 minutes. Allow the mixture to cool to room temperature and dilute to 10 mL. Further cool the mixture to below 10° and filter (0.7-µm GMF Syringe filter is suitable), discarding the first few mL of filtrate, and allow to reach room temperature.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dissolve the contents of a vial of *fusidic acid impurity mixture EPCRS* in 1.0 mL of solution A.

(4) 0.2% w/v of *fusidic acid for peak identification EPCRS*.

(5) 0.0005% w/v of *butylhydroxyanisole*.

(6) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of *methanol*, 40 volumes of *acetonitrile* and 40 volumes of 0.05M *orthophosphoric acid*.

Mobile phase B 20 volumes of *methanol*, 70 volumes of *acetonitrile*, and 10 volumes of 0.05M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-33	0	100	isocratic

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
33-34	0→100	100→0	linear gradient
34-40	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to fusidic acid (retention time about 18 minutes) are: butylhydroxyanisole, about 0.38; impurity A, about 0.4; impurity B, about 0.5; impurity C, about 0.6; impurity D, about 0.63; impurity N about 0.65; impurity F, about 0.7; impurity G, about 0.8; impurity H, about 0.9; impurity I, about 0.96; impurity K, about 1.18; impurity L, about 1.23 and impurity M, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurities G and H is at least 1.5.

LIMITS

Identify any peaks due to impurities C, D, F, G, I, K and M using relative retentions and the chromatograms obtained with solutions (3) and (4). Multiply the area of the peaks by the following correction factors: impurities C and D, 0.7; impurity F, 0.3; and impurities I and K, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the area of any peak due to impurity G is not greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%);

the area of any other secondary peak is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any secondary peaks is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

Disregard any peak due to butylhydroxyanisole, any peak that elutes before the retention time of this peak, and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in Solution A as described under Related substances.

(1) Disperse a quantity of the cream containing the equivalent of 25 mg of anhydrous fusidic acid in 8 mL of solution A, heat the mixture until the cream has melted and shake vigorously for 15 minutes. Cool the mixture to room temperature and dilute to 100 ml. Further cool the mixture to below 10° and filter (0.7-µm GMF Syringe filter is suitable), discarding the first few mL of filtrate, and allow to reach room temperature.

(2) 0.03% w/v of *diethanolamine fusidate BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used with the following modification.

MOBILE PHASE

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-29	0→100	100→0	linear gradient
29-35	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the retention time of fusidic acid is about 18 minutes.

DETERMINATION OF CONTENT

Calculate the content of fusidic acid, $C_{31}H_{48}O_6$ in the cream using the chromatograms obtained and the declared content of $C_{31}H_{48}O_6$ in *diethanolamine fusidate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous fusidic acid.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Fusidic Acid.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fusidic Acid Eye Drops

General Notices

Action and use

Antibacterial.

DEFINITION

Fusidic Acid Eye Drops are a sterile suspension of Fusidic Acid in a suitable vehicle.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of anhydrous fusidic acid, $C_{31}H_{48}O_6$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse, with shaking, a quantity of the eye drops containing the equivalent of 20 mg of anhydrous fusidic acid in 10 mL of *ethanol (70%)*, filter and use the filtrate.

(2) 0.25% w/v of *diethanolamine fusidate BPCRS* in *ethanol (70%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254}* plate (Merck silica gel 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 12.5 cm.

(e) After removal of the plate, dry in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2.5 volumes of *methanol*, 10 volumes of *glacial acetic acid*, 10 volumes of *cyclohexane* and 80 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to fusidic acid in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Acidity

pH, 5.2 to 6.2, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in Solution A.

Solution A 10 volumes of *methanol*, 40 volumes of a 0.05M solution of *orthophosphoric acid* and 50 volumes of *acetonitrile*.

(1) Disperse a quantity of the eye drops containing the equivalent of 25 mg of anhydrous fusidic acid in 6 mL of solution A and shake vigorously for 15 minutes, dilute to 10 mL. Add 0.5 g of *potassium nitrate*, shake for 5 minutes and filter (0.7-µm glass microfiber syringe is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dissolve the contents of a vial of *fusidic acid impurity mixture EPCRS* in 1.0 mL of solution A.

(4) 0.2% w/v of *fusidic acid for peak identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of *methanol*, 40 volumes of *acetonitrile* and 40 volumes of 0.05M *orthophosphoric acid*.

Mobile phase B 20 volumes of *methanol*, 70 volumes of *acetonitrile*, and 10 volumes of 0.05M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-33	0	100	isocratic
33-34	0→100	100→0	linear gradient
34-40	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to fusidic acid (retention time about 18 minutes) are: impurity A, about 0.4; impurity B, about 0.5; impurity C, about 0.6; impurity D, about 0.63; impurity N about 0.65;

www.webofpharma.com

https://nhathuocngocanh.com/

impurity F, about 0.7; impurity G, about 0.8; impurity H, about 0.9; impurity I, about 0.96; impurity K, about 1.18; impurity L, about 1.23 and impurity M, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurities G and H is at least 1.5.

LIMITS

Identify any peaks due to impurities C, D, F, G, I, K and M using relative retentions and the chromatograms obtained with solutions (3) and (4). Multiply the area of the peaks by the following correction factors: impurities C and D, 0.7; impurity F, 0.3; and impurities I and K, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity I is not greater than 1.1 times the area of the principal peak in the chromatogram obtained with solution (2) (1.1%);

the area of any peaks due to impurities G and M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak due to impurity L is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other secondary peak is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any secondary peaks is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in Solution A as described under Related substances.

(1) Disperse a weighed quantity of the eye drops containing the equivalent of 25 mg of anhydrous fusidic acid in 8 mL of solution A, shake vigorously for 15 minutes, and dilute to 100 ml. Add 0.5g of *potassium nitrate*, shake for 5 minutes and filter (0.7-µm glass microfiber syringe is suitable), discarding the first few mL of filtrate.
(2) 0.03% w/v of *diethanolamine fusidate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used with the following modification.

MOBILE PHASE

www.webofpharma.com

https://thuvienthuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-29	0→100	100→0	linear gradient
29-35	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the retention time of fusidic acid is about 18 minutes.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the eye drops, Appendix V G, and calculate the content of $C_{31}H_{48}O_6$ weight in volume, using the declared content of $C_{31}H_{48}O_6$ in *diethanolamine fusidate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous fusidic acid.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Fusidic Acid.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Fusidic Acid Oral Suspension

General Notices

Action and use

Antibacterial.

DEFINITION

Fusidic Acid Oral Suspension is a suspension of Fusidic Acid in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of anhydrous fusidic acid, $C_{31}H_{48}O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity containing the equivalent of 0.1 g of anhydrous fusidic acid add 5 mL of *water* and extract with three 10-mL quantities of *dichloromethane*. Wash the combined extracts with two 10-mL quantities of *water*, dry with *anhydrous sodium sulfate*, evaporate to dryness and dissolve the residue in 1 mL of *dichloromethane*. The *infrared absorption spectrum* of the resulting solution, Appendix II A, is concordant with the *reference spectrum* of fusidic acid *(RS 166)*.

TESTS

Acidity

pH, 4.8 to 5.2, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in Solution A.

Solution A 10 volumes of *methanol*, 40 volumes of 0.05M *orthophosphoric acid* and 50 volumes of *acetonitrile*.

(1) Extract a quantity of the oral suspension containing the equivalent of 25 mg of anhydrous fusidic acid with two 10-mL quantities of *dichloromethane*, evaporate the combined extracts to dryness and dissolve the residue in 10 mL of solution A.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) Dissolve the contents of a vial of *fusidic acid impurity mixture EPCRS* in 1.0 mL of solution A.

(4) 0.2% w/v of *fusidic acid for peak identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Symmetry C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 235 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of *methanol*, 40 volumes of *acetonitrile* and 40 volumes of 0.05M *orthophosphoric acid*.

Mobile phase B 20 volumes of *methanol*, 70 volumes of *acetonitrile*, and 10 volumes of 0.05M *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-33	0	100	isocratic
33-34	0→100	100→0	linear gradient
34-40	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to fusidic acid (retention time about 18 minutes) are: impurity A, about 0.4; impurity B, about 0.5; impurity C, about 0.6; impurity D, about 0.63; impurity N about 0.65; impurity F, about 0.7; impurity G, about 0.8; impurity H, about 0.9; impurity I, about 0.96; impurity K, about 1.18; impurity L, about 1.23 and impurity M, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurities G and H is at least 1.5.

LIMITS

Identify any peaks due to impurities C, D, F, G, I, K and M using relative retentions and the chromatograms obtained with solutions (3) and (4). Multiply the area of the peaks by the following correction factors: impurities C and D, 0.7; impurity F, 0.3; and impurities I and K, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity G is not greater than 1.1 times the area of the principal peak in the chromatogram obtained with solution (2) (1.1%);

the area of any peak due to impurity M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak due to impurity F is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak due to impurity A, B, C, D, I, K or L is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in Solution A as described under Related substances.

(1) Extract a weighed quantity of the oral suspension containing the equivalent of 25 mg of anhydrous fusidic acid with two 40-mL quantities of *dichloromethane*, evaporate the combined extracts to dryness, dissolve the residue in solution A and dilute to 100 mL.
(2) 0.03% w/v of *diethanolamine fusidate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used with the following modification.

MOBILE PHASE

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	100	0	isocratic
3-28	100→0	0→100	linear gradient
28-29	0→100	100→0	linear gradient
29-35	100	0	re-equilibration

When the chromatograms are recorded using the prescribed conditions, the retention time of fusidic acid is about 18 minutes.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{31}H_{48}O_6$ weight in volume, using the declared content of $C_{31}H_{48}O_6$ in *diethanolamine fusidate BPCRS*.

STORAGE

Fusidic Acid Oral Suspension should be protected from light.

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous fusidic acid.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Fusidic Acid.

© Crown Copyright 2022

www.webofpharma.com

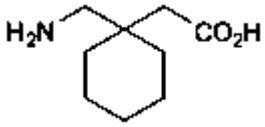
https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gabapentin

General Notices

(Ph. Eur. monograph 2173)



$C_9H_{17}NO_2$ 171.2 *60142-96-3*

Action and use

Antiepileptic.

Preparations

Gabapentin Capsules

Gabapentin Oral Solution

Gabapentin Tablets

Ph Eur

DEFINITION

[1-(Aminomethyl)cyclohexyl]acetic acid.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

www.webofpharma.com

https://thuocngocanh.com/

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *gabapentin CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 1.50 g in a mixture of 0.5 mL of *acetic acid R*, 19.5 mL of *methanol R* and 30 mL of *water R*.

pH (2.2.3)

6.5 to 7.5.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Related substances

A. Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Solution A Dissolve 2.32 g of *ammonium dihydrogen phosphate R* in 950 mL of *water R*, adjust to pH 2.0 with *phosphoric acid R*, and dilute to 1000 mL with *water R*.

Buffer solution Dissolve 0.58 g of *ammonium dihydrogen phosphate R* and 1.83 g of *sodium perchlorate R* in 950 mL of *water for chromatography R*, adjust to pH 1.8 with *perchloric acid R*, and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 0.140 g of the substance to be examined in solution A and dilute to 10.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 7.0 mg of *gabapentin impurity A CRS* and 10 mg of *gabapentin impurity B CRS* in *methanol R1* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with solution A.

Reference solution (c) Dissolve 0.140 g of *gabapentin CRS* in solution A and dilute to 10.0 mL with solution A.

Reference solution (d) Dissolve 7.0 mg of *gabapentin impurity D CRS* in 25 mL of *methanol R1* and dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R1*, buffer solution (24:76 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time 4 times the retention time of gabapentin.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to gabapentin (retention time = about 4 min): impurity A = about 2.4; impurity B = about 2.8.

System suitability Reference solution (b):

— *resolution*: minimum 2.3 between the peaks due to impurities A and B.

To avoid memory effects between 2 chromatograms, the column may be washed using *acetonitrile R1*.

Limits:

— *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply for this test.

B. Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modifications.

Mobile phase *methanol R2*, *acetonitrile R1*, buffer solution (30:35:35 *V/V/V*).

Injection 20 µL of the test solution and reference solution (d).

Run time 1.2 times the retention time of impurity D.

Retention time Impurity D = about 10 min.

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent);

— *disregard limit*: 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.03 per cent); disregard any peak with a relative retention of not more than 0.4 with reference to impurity D.

Limit:

— *total for tests A and B*: maximum 0.5 per cent.

Chlorides

Maximum 100 ppm.

Dissolve 1.5 g in a mixture of 0.5 mL of *acetic acid R*, 19.5 mL of *methanol R* and 30 mL of *water R*. Titrate with *0.001 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.001 M silver nitrate* is equivalent to 0.03545 mg of chlorides.

Water (*2.5.32*)

Maximum 0.3 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in test A for related substances with the following modification.

Injection 20 µL of the test solution and reference solution (c).

System suitability Reference solution (c):

— *symmetry factor*: maximum 5.0 for the peak due to gabapentin.

Calculate the percentage content of $C_9H_{17}NO_2$ taking into account the assigned content of *gabapentin CRS*.

IMPURITIES

Test A for related substances

A, B, E, G.

Test B for related substances

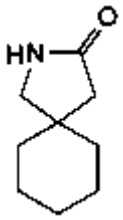
D.

www.webofpharma.com

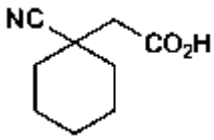
https://thuocngocanh.com/

Specified impurities *A*.

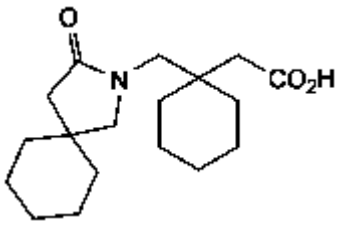
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E, G*.



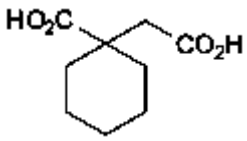
A. 2-azaspiro[4.5]decan-3-one,



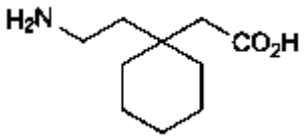
B. (1-cyanocyclohexyl)acetic acid,



D. [1-[(3-oxo-2-azaspiro[4.5]dec-2-yl)methyl]cyclohexyl]acetic acid,



E. 1-(carboxymethyl)cyclohexanecarboxylic acid,



G. [1-(2-aminoethyl)cyclohexyl]acetic acid.

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thietbiuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gabapentin Capsules

General Notices

Action and use

Antiepileptic

DEFINITION

Gabapentin Capsules contain Gabapentin.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of gabapentin, $C_9H_{17}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum* of the content of the capsules collected in ATR mode, Appendix II A, is concordant with the *reference spectrum* obtained with *gabapentin EPCRS*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, *Appendix XII B1*.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium, filter and dilute the filtrate with dissolution medium, if necessary, to produce a solution expected to contain 0.011% w/v of Gabapentin.

(2) 0.011% w/v of *gabapentin EPCRS* in the medium.

(3) 0.033% w/v of *gabapentin EPCRS* and 0.0016% w/v of *gabapentin impurity A EPCRS* in the medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5 µm) (Hypersil ODS is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

1 volume of *orthophosphoric acid*, 22 volumes of *acetonitrile R1*, 78 volumes of *methanol R1* and 115 volumes of a solution containing 1% w/v of *ammonium dihydrogen orthophosphate* and 0.17% w/v of *sodium decanesulfonate* in *water*. Adjust the pH to 4.4 with *triethylamine*.

When the chromatograms are recorded under the prescribed conditions, the retention times of gabapentin and impurity A is about 6 minutes and 8.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gabapentin impurity A and gabapentin is at least 5.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_9H_{17}NO_2$ in the medium from the chromatograms obtained and using the declared content of $C_9H_{17}NO_2$ in *gabapentin EPCRS*.

LIMITS

The amount of gabapentin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *acetonitrile R1* and 9 volumes of *water* (solvent A).

(1) Dissolve a quantity of the contents of the capsules containing 0.5 g of Gabapentin in 20 mL of solvent A. Add a sufficient volume of the solvent A to produce 25 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 10 volumes.

(3) 0.02% w/v each of *gabapentin EPCRS*, *gabapentin impurity A EPCRS* and *gabapentin impurity B EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *dimethyloctylsilane* (5 µm) (Hypersil MOS-2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase A 0.01M *potassium dihydrogen orthophosphate* previously adjusted to pH 6.9 with a 10% w/v solution of *potassium hydroxide*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0→5	100	0	isocratic
5→15	100→90	0→10	linear gradient
15→45	90→70	10→30	linear gradient
45→55	70→25	30→75	linear gradient
55→60	25	75	isocratic
60→61	25→100	75→0	linear gradient
61→70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to gabapentin (retention time about 14 minutes) are: impurity B, about 1.1; impurity A, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gabapentin and gabapentin impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to gabapentin impurity A is not more than 0.4 times the area of the corresponding peak in the chromatogram obtained with solution (3) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peak* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Mix and powder the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase.

www.webofpharma.com

https://thietbiuocngocanh.com/

(1) Mix with the aid of ultrasound, a quantity of the powdered contents of the capsules containing 1.25 g of Gabapentin with 150 mL of mobile phase. Add sufficient mobile phase to produce 200 mL and filter.

(2) 0.625% w/v of *gabapentin EPCRS*.

(3) 0.032% w/v each of *gabapentin EPCRS* and *gabapentin impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (10 µm) (Lichrosorb RP-18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

10 volumes of *acetonitrile R1*, 35 volumes of *methanol R1*, 55 volumes of *water* and 0.1 volumes of a mixture containing 0.35% w/v of *potassium dihydrogen orthophosphate* and 0.73% w/v of *disodium hydrogen orthophosphate* previously adjusted to pH 7.0 with either *orthophosphoric acid* or a 10% w/v solution of *potassium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention times of gabapentin and impurity A are about 3 minutes and 10 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gabapentin and impurity A is at least 10.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{17}NO_2$ in the capsules using the declared content of gabapentin in *gabapentin EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and E listed under Gabapentin.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thietbiuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gabapentin Oral Solution

General Notices

Action and use

Antiepileptic.

DEFINITION

Gabapentin Oral Solution contains Gabapentin.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of gabapentin, $C_9H_{17}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *methanol*.

(1) Dilute a quantity of the oral solution to produce a solution containing 0.025% w/v of Gabapentin.

(2) 0.025% w/v of *gabapentin EPCRS*.

(3) 0.025% w/v each of *gabapentin EPCRS* and *vigabatrin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry at 105°, spray with *ninhydrin solution R4* and heat at 105° for 2 minutes. Examine in daylight.

MOBILE PHASE

2 volumes of *methanol*, 3 volumes of *acetonitrile* and 15 volumes of 0.05M *potassium dihydrogen orthophosphate*, adjusted to pH 6.3 with *potassium hydroxide solution*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 7.5, Appendix V L.

Gabapentin impurity A

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute a quantity of the oral solution to produce a solution containing 0.25% w/v of Gabapentin.
(2) 0.001% w/v of *gabapentin impurity A EPCRS*.
(3) 0.05% w/v of each of *methyl 4-hydoxybenzoate* and *gabapentin impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 2.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (1.7 µm) (Kinetex C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.4 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 1.5 µL of each solution.

MOBILE PHASE

95 volumes of *acetonitrile R1* and 405 volumes of a 0.154% w/v solution of *ammonium acetate* in *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to methyl 4-hydrozybenzoate and gabapentin impurity A is not less than 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.4%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Dilute a quantity of the oral solution to produce a solution containing 0.5% w/v of Gabapentin.
(2) Dilute 1 volume of solution (1) to 100 volumes and dilute 1 volume of the resulting solution to 10 volumes.
(3) 0.05% w/v each of *gabapentin EPCRS* and *gabapentin impurity B EPCRS*.

www.webofpharma.com

https://thietbiuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.0 mm) packed with *end-capped phenylethyl* *silica gel for chromatography* (4 µm) (Synergi Polar RP is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 50°.

(e) Use evaporative light scattering detection using a flow rate of 1.3 litres per minute and an evaporator temperature of 60°.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.063% w/v of *ammonium formate* in *water*, adjusted to pH 3.2 with *formic acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	99	1	isocratic
1-7	99→40	1→60	linear gradient
7-8	40	60	isocratic
8-9	40→99	60→1	linear gradient
9-18	99	1	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gabapentin and impurity B is not less than 6.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than 10 times the area of the principal peak if the chromatogram obtained with solution (2) (1.0%);

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute a weighed quantity of the oral solution with sufficient *water* to produce a solution containing 0.25% w/v of Gabapentin.

www.webofpharma.com

https://thietbiuocngocanh.com/

(2) 0.25% w/v of *gabapentin EPCRS* in *water*.

(3) 0.25% w/v of *gabapentin EPCRS* and 0.06% w/v of *methyl parahydroxybenzoate* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Eclipse XDB C-18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 211 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

2.5 volumes of *orthophosphoric acid*, 200 volumes of *acetonitrile R1* and 800 volumes of 0.006M *sodium heptanesulfonate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gabapentin and methyl parahydroxybenzoate is at least 10.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_9H_{17}NO_2$, weight in volume, using the declared content of $C_9H_{17}NO_2$ in *gabapentin EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A and B listed under Gabapentin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gabapentin Tablets

General Notices

Action and use

Antiepileptic.

DEFINITION

Gabapentin Tablets contain Gabapentin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of gabapentin, $C_9H_{17}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

The *infrared absorption spectrum* of the powdered tablets collected in ATR mode, Appendix II A, is concordant with the *reference spectrum* obtained with *gabapentin EPCRS*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with dissolution medium if necessary, to produce a solution expected to contain 0.011% w/v of Gabapentin.

(2) 0.011% w/v of *gabapentin EPCRS* in 0.1M *hydrochloric acid*.

(3) 0.033% w/v of *gabapentin EPCRS* and 0.0016% w/v of *gabapentin impurity A EPCRS* in the medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5 µm) (Hypersil ODS is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

1 volume of *orthophosphoric acid*, 22 volumes of *acetonitrile R1*, 78 volumes of *methanol R1* and 115 volumes of a solution containing 1% w/v of *ammonium dihydrogen orthophosphate* and 0.17% w/v of *sodium decanesulfonate* in *water*. Adjust the pH to 4.4 with *triethylamine*.

When the chromatograms are recorded under the prescribed conditions, the retention times of gabapentin and impurity A is about 6 minutes and 8.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gabapentin impurity A and gabapentin is at least 5.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_9H_{17}NO_2$ in the medium from the chromatograms obtained and using the declared content of $C_9H_{17}NO_2$ in *gabapentin EPCRS*.

LIMITS

The amount of gabapentin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *acetonitrile R1* and 9 volumes of *water* (solvent A).

(1) Disperse a quantity of powdered tablets containing 0.5 g of Gabapentin in 20 mL of solvent A. Add a sufficient volume of the solvent A to produce 25 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes, dilute 1 volume of the resulting solution to 10 volumes.

(3) 0.02% w/v each of *gabapentin EPCRS*, *gabapentin impurity A EPCRS* and *gabapentin impurity B EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *dimethyloctylsilane* (5 µm) (Hypersil MOS is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thietbiuocngocanh.com/

Mobile phase A 0.01M *potassium dihydrogen orthophosphate* previously adjusted to pH 6.9 with a 10% w/v solution of *potassium hydroxide*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0→5	100	0	isocratic
5→15	100→90	0→10	linear gradient
15→45	90→70	10→30	linear gradient
45→55	70→25	30→75	linear gradient
55→60	25	75	isocratic
60→61	25→100	75→0	linear gradient
61→70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to gabapentin (retention time about 14 minutes) are: impurity B, about 1.1; impurity A, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to and gabapentin and gabapentin impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to gabapentin impurity A is not greater than 0.4 times the area of the corresponding peak in the chromatogram obtained with solution (3) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peak* is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 1.25 g of Gabapentin in 150 mL of mobile phase, add sufficient mobile phase to produce 200 mL and filter.

www.webofpharma.com

https://thietbiuocngocanh.com/

(2) 0.625% w/v of *gabapentin EPCRS* in mobile phase.

(3) 0.032% w/v each of *gabapentin EPCRS* and *gabapentin impurity A EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilylsilica gel* (10 µm) (µBondapak C-18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

10 volumes of *acetonitrile R1*, 35 volumes of *methanol R1*, 55 volumes of *water* and 0.1 volumes of a mixture containing 0.35% w/v of *potassium dihydrogen orthophosphate* and 0.73% w/v of *disodium hydrogen orthophosphate* previously adjusted to pH 7.0 with either *orthophosphoric acid* or a 10% w/v solution of *potassium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention times of gabapentin and impurity A are about 3 minutes and 10 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gabapentin and impurity A is at least 10.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_{17}NO_2$ in the tablets using the declared content of gabapentin in *gabapentin EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and E listed under Gabapentin.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thietbiuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

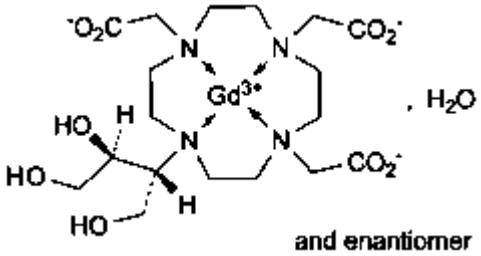
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gadobutrol Monohydrate

General Notices

(Ph. Eur. monograph 2735)



$C_{18}H_{31}GdN_4O_9,H_2O$ 623 *198637-52-4*

Action and use

Paramagnetic contrast medium

Ph Eur

DEFINITION

Gadolinium 2,2′,2″-[10-[(1*RS*,2*SR*)-2,3-dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triyl]triacetate monohydrate.

Content

— *gadobutrol*: 97.5 per cent to 102.5 per cent (anhydrous substance);

— *gadolinium*: 98.0 per cent to 102.0 per cent, calculated as gadobutrol (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water, practically insoluble in anhydrous ethanol and in heptane.

It shows polymorphism (5.9).

IDENTIFICATION

www.webofpharma.com

https://thietbiuocngocanh.com/

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *gadobutrol monohydrate CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in 0.5 mL of *water R*, then add 5 mL of *anhydrous ethanol R*; evaporate to dryness and record new spectra using the residues.

B. Inductively coupled plasma-atomic emission spectrometry (2.2.57) as described in the assay for gadolinium.

TESTS

Specific optical rotation (2.2.7)

-0.05 to + 0.05 (anhydrous substance), using an instrument with a minimum sensitivity of ± 0.002°.

Dissolve 6.00 g in *water R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Use suitable plastic labware for the preparation of the solutions and plastic vials. Store the solutions at 10 °C and use them within 42 h.*

Test solution (a) Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 5.0 mL with mobile phase A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve 10 mg of *gadobutrol for peak identification CRS* (containing impurity C) in 1 mL of mobile phase A.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase A.

Reference solution (c) Dissolve 50.0 mg of *gadobutrol monohydrate CRS* in mobile phase A and dilute to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped phenylhexylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 5 volumes of *acetonitrile R1* and 995 volumes of *water for chromatography R* previously adjusted to pH 3.6 with a 50 per cent *V/V* solution of *anhydrous formic acid R* in *water for chromatography R*;

— *mobile phase B*: *acetonitrile R1*;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 30	100 → 75	0 → 25

Flow rate 1.0 mL/min.

Detection Charged aerosol detector at 100 pA.

Autosampler Set at 10 °C.

Injection 40 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *gadobutrol for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity C.

Relative retention With reference to gadobutrol (retention time = about 11 min): impurity C = about 1.2.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to gadobutrol.

Calculation of percentage contents:

— for each impurity, use the concentration of gadobutrol monohydrate in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.03 per cent.

Free gadolinium

Maximum 0.01 per cent (anhydrous substance).

Solution A To 30.0 mL of *sodium acetate buffer solution pH 5.0 R* add 3.0 mL of *xylenol orange solution R* and dilute to 200.0 mL with *water R*.

Gadolinium sulfate solution Dissolve 93.35 mg of *gadolinium sulfate octahydrate R* in *water R* and dilute to 1000.0 mL with the same solvent.

Test solution Dissolve 0.250 g of the substance to be examined in 5.0 mL of the gadolinium sulfate solution and 30 mL of *water R* with the aid of ultrasound. Add 10.0 mL of solution A and adjust to pH 5.0 with a 10.3 g/L solution of *hydrochloric acid R*. Titrate with *0.00025 M*

www.webofpharma.com

https://thuocngocanh.com/

sodium edetate, determining the end-point photometrically using a suitable autotitrator equipped with a photometric sensor at a wavelength of 570-574 nm (V_1 mL).

Standard solution Prepare a solution in the same manner as for the test solution but omitting the substance to be examined (V_2 mL).

Determine the free gadolinium content from the difference in the volumes of titrant consumed (V_1 - V_2).

1 mL of *0.00025 M sodium edetate* is equivalent to 0.03931 mg of gadolinium.

Water (*2.5.32*)

2.0 per cent to 7.0 per cent, determined on 0.100 g using the evaporation technique at 220 °C.

ASSAY

Gadobutrol

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Detection Spectrophotometer at 195 nm.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{18}H_{31}GdN_4O_9$ taking into account the assigned content of *gadobutrol monohydrate CRS*.

Gadolinium

Inductively coupled plasma-atomic emission spectrometry (*2.2.57*).

Yttrium standard solution To 100.0 mL of a certified reference solution containing 1000 mg/L of Y add 50 mL of *nitric acid R* and dilute to 1000.0 mL with *water R*.

Zero solution To 1.5 mL of the yttrium standard solution add 0.5 mL of *nitric acid R* and dilute to 50.0 mL with *water R*.

Test solution Dissolve 50.0 mg of the substance to be examined in 150.0 mL of *water R*, add 7.5 mL of yttrium standard solution and 2.0 mL of *nitric acid R* and dilute to 250.0 mL with *water R*.

Reference solutions Into 3 volumetric flasks introduce respectively 2.0 mL, 2.5 mL and 3.0 mL of a certified reference solution containing 1000 mg/L of Gd. To each flask add 1.5 mL of the yttrium standard solution and 0.5 mL of *nitric acid R* and dilute to 50.0 mL with *water R*.

Wavelengths 217.069 nm, 217.774 nm, 219.103 nm, 226.109 nm (gadolinium), 224.306 nm (yttrium).

From the calibration curve obtained with the reference solutions, calculate the percentage content of gadolinium in the substance to be examined, using the mean of the results obtained with the different wavelengths and applying a conversion factor of 3.846.

STORAGE

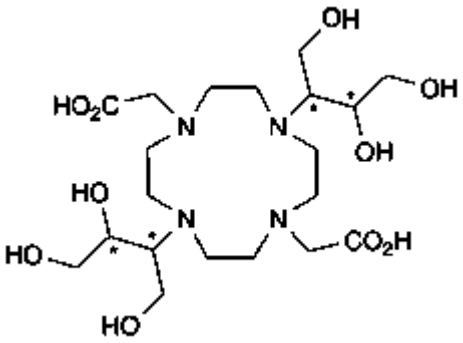
In an airtight container, protected from light.

www.webofpharma.com

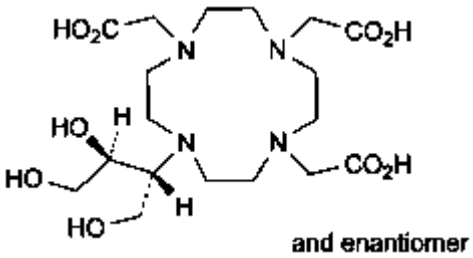
https://thuocngocanh.com/

IMPURITIES

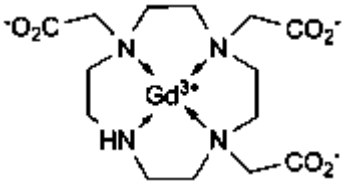
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C.*



A. 2,2′-[4,10-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,7-diyl]diacetic acid,



B. 2,2′,2″-[10-[(1*RS*,2*SR*)-2,3-dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triyl]triacetic acid,



C. gadolinium 2,2′,2″-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thietbiuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

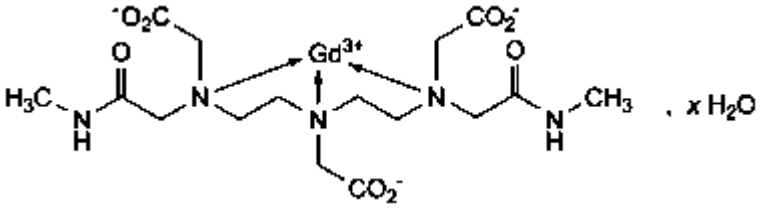
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Gadodiamide Hydrate

General Notices

(Ph. Eur. monograph 2225)



$C_{16}H_{26}GdN_5O_8,xH_2O$ with x = 2 to 5 573.7 (anhydrous substance)

Anhydrous gadodiamide *131410-48-5*

Action and use

Paramagnetic contrast enhancing medium for magnetic resonance imaging.

Ph Eur

DEFINITION

6-(Carboxylatomethyl)-3,9-bis[(methylcarbamoyl)methyl]-3,6,9-triazaundecanedioato-κ$^3N^3$,N^6,N^9-gadolinium(III) hydrate (Gd-DTPA-BMA).

Content

— *gadolinium* (Gd; M_r 157.3): 26.0 per cent to 29.0 per cent (anhydrous substance);

— *gadodiamide* ($C_{16}H_{26}GdN_5O_8$; M_r 573.7): 96.5 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or almost white powder, slightly hygroscopic.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Freely soluble in water and in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *gadodiamide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Gadolinium (see Assay).

Results The test solution exhibits the characteristic emission of gadolinium at 342.247 nm.

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*). If this is not the case, heat the solution at 60-70 °C for 2-3 min, cool to room temperature and compare the solutions again.

Dissolve 7.5 g (anhydrous substance) in *water R* and dilute to 25 mL with the same solvent.

pH (*2.2.3*)

4.0 to 6.5.

Dissolve 0.50 g (anhydrous substance) in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 0.200 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Test solution (b) Dissolve 60.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 5.0 mg of *gadodiamide impurity A CRS* and 5.0 mg of *gadodiamide impurity B CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (b) Dissolve 20 mg of *gadodiamide CRS* in *water R*, add 0.5 mL of reference solution (a) and dilute to 10 mL with *water R*.

Reference solution (c) Dissolve 60.0 mg of *gadodiamide CRS* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (d) Dilute 1.0 mL of test solution (a) to 50.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (e) Dilute 1.0 mL of reference solution (a) to 20.0 mL with *water R*.

www.webofpharma.com

https://thietbiuocngocanh.com/

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase To 980 mL of *water for chromatography R* add 287 µL of *glacial acetic acid R* and 700 µL of *triethylamine R*, adjust to pH 6.8 with a 0.6 g/L solution of *acetic acid R* or with a 42 g/L solution of *sodium hydroxide R*, then dilute to 1000 mL with *water for chromatography R*; use within 2 days.

Flow rate 1.5 mL/min.

Post-column solution Dissolve 0.120 g of *arsenazo III R* in about 400 mL of *water for chromatography R*, add 0.650 g of *urea R* and mix to dissolve; add 6.3 mL of *nitric acid R* and sonicate for 15 min, filter through a membrane filter (nominal pore size 0.45 µm) and wash the filter with about 550 mL of *water for chromatography R*; dilute the filtrate and washings to 1000 mL with *water for chromatography R*; use within 1 week.

Flow rate of post-column solution 1.5 mL/min.

Detection Spectrophotometer at 658 nm.

Injection 10 µL of test solution (a) and reference solutions (b), (d) and (e).

Run time 5 times the retention time of gadodiamide.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to gadodiamide (retention time = about 5 min): impurity A = about 2.6; impurity B = about 4.0. The peak due to gadodiamide shows a shoulder due to an isomer that is to be integrated with the main peak.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to gadodiamide and impurity A; minimum 2.5 between the peaks due to impurities A and B.

Calculation of percentage contents:

— for impurities A and B, use the concentration of each substance in reference solution (e);

— for impurities other than A and B, use the concentration of gadodiamide hydrate in reference solution (d).

Limits:

— *impurity A*: maximum 1.0 per cent;

— *impurity B*: maximum 0.2 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *sum of unspecified impurities*: maximum 0.3 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.10 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Excess of gadolinium or DTPA-BMA

Maximum 20 ppm (anhydrous substance) for the excess of gadolinium and maximum 0.1 per cent (anhydrous substance) for the excess of diethylenetriaminepentaacetic acid bis-(methylamide) (DTPA-BMA).

Test solution Dissolve 2.0 g of the substance to be examined in 25.0 mL of *1 M morpholinoethanesulfonate buffer solution pH 6.0 R*. Add 50 µL of a 1.5 g/L solution of *arsenazo III R*.

Blank solution To 25.0 mL of *1 M morpholinoethanesulfonate buffer solution pH 6.0 R*, add 50 µL of a 1.5 g/L solution of *arsenazo III R*. The solution is violet-pink.

Standard solution Dissolve 18.6 g of *gadolinium chloride hexahydrate R* in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 1000.0 mL with the same acid solution. Dilute 20.0 mL of this solution to 1000.0 mL with *water R* (0.001 M solution). Standardise 10.0 mL of *0.001 M sodium edetate*, using a mixture of 25.0 mL of *1 M morpholinoethanesulfonate buffer solution pH 6.0 R* and 50 µL of a 1.5 g/L solution of *arsenazo III R*. Titrate with the standard solution until a greenish-blue colour is obtained.

Excess of DTPA-BMA If the test solution is violet-pink, there is no excess of gadolinium. Determine the excess of DTPA-BMA by titrating the test solution and the blank solution with the standard solution until a greenish-blue colour is obtained. Calculate the excess of DTPA-BMA, in per cent, using the following expression:

$$\frac{\left(V_1 - V_0\right) \times M_1 \times 419.43 \times 100}{m}$$

V_0 = volume of standard solution used in the blank titration, in millilitres;

V_1 = volume of standard solution used in the titration of the test solution, in millilitres;

M_1 = molarity of the gadolinium solution, in moles per litre;

m = mass of the substance to be examined (anhydrous substance) used to prepare the test solution, in milligrams.

Excess of gadolinium If the test solution is greenish-blue, there is no excess of DTPA-BMA. Determine the excess of gadolinium by titrating the test solution with *0.001 M sodium edetate* until a violet-pink colour is obtained. Calculate the excess of gadolinium, in parts per million, using the following expression:

$$\frac{V_2 \times M_2 \times 157.25 \times 10^6}{m}$$

www.webofpharma.com

https://thietbiuocngocanh.com/

V_2 = volume of *0.001 M sodium edetate* used in the titration of the test solution, in millilitres;

M_2 = molarity of the sodium edetate solution, in moles per litre;

m = mass of the substance to be examined (anhydrous substance) used to prepare the test solution, in milligrams.

Impurity C

Maximum 0.02 per cent (anhydrous substance).

Phthalaldehyde solution Introduce 0.100 g of *phthalaldehyde R* into a brown-glass vessel and dissolve in 3 mL of *methanol R*. Add 220 mL of *borate buffer solution pH 10.0 R* and 100 µL of *2-mercaptoethanol R* and mix. Keep refrigerated and use within 24 h.

Test solution Dissolve 1.5 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solutions Prepare a series of reference solutions for calibration in the range of 1 µg/mL to 35 µg/mL of methylamine (impurity C) from a 0.220 g/L solution of *methylamine hydrochloride R*. Calculate the concentrations of methylamine by multiplying the concentrations of methylamine hydrochloride by 0.46.

Blank solution A freshly prepared mixture of 3.0 mL of phthalaldehyde solution and 3.0 mL of *water R*.

Introduce 3.0 mL of the test solution and of each reference solution into separate test tubes. Add 3.0 mL of phthalaldehyde solution to each tube and mix. Immediately transfer each solution to a cell and immediately measure the absorbance (*2.2.25*) at 335 nm using the blank solution as compensation liquid. Calculate the linear regression curve from the absorbances obtained with the reference solutions: the coefficient of determination r^2 is not less than 0.99. If the absorbance obtained with the test solution is outside the calibration range, dilute the test solution with *water R* and repeat the procedure.

Water (*2.5.12*)

6.0 per cent to 13.0 per cent, determined on 0.150 g.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Bacterial endotoxins (*2.6.14*)

Less than 3.50 IU/g.

ASSAY

Gadolinium

Inductively coupled plasma-atomic emission spectrometry (*2.2.57*). An external calibration curve is used for quantification.

Test solution Dissolve 0.600 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with a 20 g/L solution of *nitric acid R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions Into 3 volumetric flasks, introduce 10.0 mL, 15.0 mL and 20.0 mL of a certified reference solution containing 1000 µg/mL of gadolinium. Dilute each flask to 100.0 mL with a 20 g/L solution of *nitric acid R*. Mix to obtain reference solutions containing respectively 100 µg/mL, 150 µg/mL and 200 µg/mL of gadolinium.

The standard operating conditions prescribed by the manufacturer of the apparatus are to be followed. The following operating conditions are cited as an example of conditions found suitable for a given apparatus:

— *flush time*: 15 s;

— *pure gas (N_2) flow*: 1 mL/min;

— *plasma flow*: 15 L/min;

— *auxiliary flow*: 1.0 mL/min;

— *nebuliser flow*: 1.0 mL/min;

— *pump rate*: 1.0 mL/min;

— *power*: 1160 W;

— *read delay*: 25 s;

— *wavelength*: 342.247 nm;

— *viewing height*: 14.0 mm;

— *background correction*: none;

— *nebuliser*: cross-flow nebuliser.

System suitability:

— the correlation coefficient of the calibration curve is not less than 0.999.

Gadodiamide

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 10 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_{16}H_{26}GdN_5O_8$ taking into account the assigned content of *gadodiamide CRS*.

STORAGE

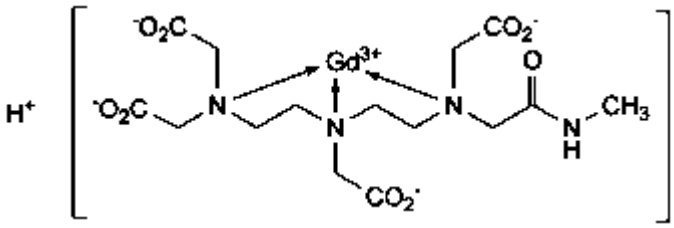
In an airtight container.

IMPURITIES

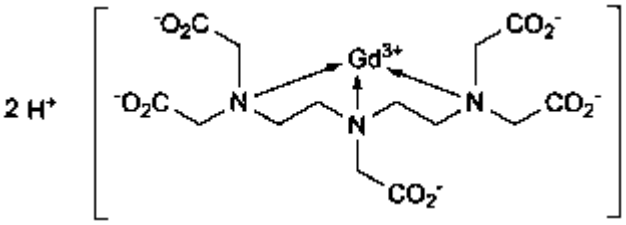
www.webofpharma.com

https://thietbiuocngocanh.com/

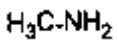
Specified impurities *A, B, C.*



A. hydrogen[3,6-bis(carboxylatomethyl)-9-[(methylcarbamoyl)methyl]-3,6,9-triazaundecanedioato-κ^3*N*^{3},*N*^{6},*N*^{9}-gadolinate](1-) (Gd-DTPA-MMA),



B. dihydrogen[3,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanedioato-κ^3*N*^{3},*N*^{6},*N*^{9}-gadolinate](2-) (Gd-DTPA),



C. methanamine (methylamine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

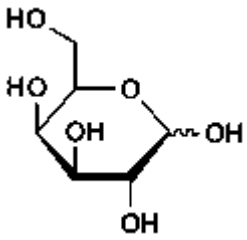
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Galactose

General Notices

(Ph. Eur. monograph 1215)



$C_6H_{12}O_6$ 180.2 *59-23-4*

Ph Eur

DEFINITION

D-Galactopyranose.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline or finely granulated powder.

Solubility

Freely soluble or soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *galactose CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of 2 volumes of water R and 3 volumes of methanol R and dilute to 20 mL with the same mixture of solvents.

Reference solution (a) Dissolve 10 mg of galactose CRS in a mixture of 2 volumes of water R and 3 volumes of methanol R and dilute to 20 mL with the same mixture of solvents.

Reference solution (b) Dissolve 10 mg each of galactose R, glucose R and lactose monohydrate R (impurity A) in a mixture of 2 volumes of water R and 3 volumes of methanol R and dilute to 20 mL with the same mixture of solvents.

Plate TLC silica gel plate R.

Mobile phase water R, propanol R (15:85 *V/V*).

Application 2 µL; thoroughly dry the points of application.

Development In an unsaturated tank over 3/4 of the plate.

Drying In a current of warm air.

Detection Spray with a solution of 0.5 g of thymol R in a mixture of 5 mL of sulfuric acid R and 95 mL of ethanol (96 per cent) R. Heat in an oven at 130 °C for 10 min.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.1 g in 10 mL of water R. Add 3 mL of cupri-tartaric solution R and heat. An orange or red precipitate is formed.

TESTS

Solution S

Dissolve, with heating in a water-bath at 50 °C, 10.0 g in carbon dioxide-free water R prepared from distilled water R and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution B_8 (2.2.2, Method II).

Acidity or alkalinity

To 30 mL of solution S add 0.3 mL of phenolphthalein solution R. The solution is colourless. Not more than 1.5 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator to pink.

www.webofpharma.com

https://thuocngocanh.com/

Proteins

Maximum 0.1 mg/mL.

Dissolve 1.000 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent. Measure the absorbance (2.2.25) of the solution at 260 nm and at 280 nm and calculate the protein content, in milligrams per millilitre, using the following expression:

$$(A_{280} \times 1.45) - (A_{260} \times 0.74)$$

A_{280} = absorbance at 280 nm;

A_{260} = absorbance at 260 nm.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.250 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 50.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *water R*.

Reference solution (b) Dissolve 3 mg each of *1,6-galactosylgalactose R* (impurity B), *galacturonic acid R* (impurity C) and *lactose monohydrate R* (impurity A) in *water R* and dilute to 10 mL with the same solvent. To 100 µL of the solution add 900 µL of test solution (a).

Reference solution (c) Dissolve 25.0 mg of *galactose CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Column 2 columns to be connected in series:

— *size*: *l* = 0.30 m, Ø = 6.5 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (10 µm);

— *temperature*: 75 °C.

Mobile phase Dissolve 50 mg of *sodium calcium edetate R* in 900 mL of *water for chromatography R*, add 1.0 mL of *sulfuric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 0.4 mL/min.

Detection Differential refractometer maintained at a constant temperature (about 40 °C).

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Run time Twice the retention time of galactose.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A + B and C.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to galactose (retention time = about 24 min): impurities A and B = about 0.8; impurity C = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity C and galactose.

Calculation of percentage contents:

— for each impurity, use the concentration of galactose in reference solution (a).

Limits:

— *sum of impurities A and B*: maximum 1.0 per cent;

— *unspecified impurities*: for each impurity, maximum 0.3 per cent;

— *total*: maximum 2.0 per cent;

— *reporting threshold*: 0.2 per cent.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g.

Sulfated ash

Maximum 0.1 per cent.

To 5 mL of solution S add 2 mL of *sulfuric acid R*, evaporate to dryness on a water-bath and ignite to constant mass. The residue weighs a maximum of 1 mg.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/g (2.6.12).

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection 10 µL of test solution (b) and reference solution (c).

Calculate the percentage content of $C_6H_{12}O_6$ taking into account the assigned content of *galactose CRS*.

IMPURITIES

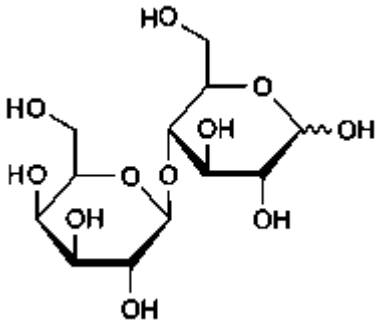
Specified impurities *A, B.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify

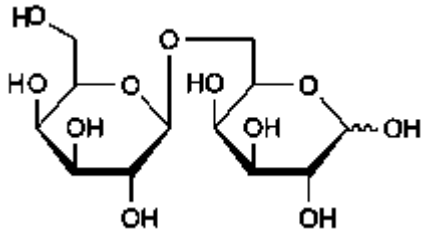
www.webofpharma.com

https://thuocngocanh.com/

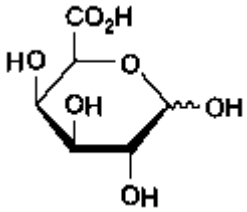
these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E.



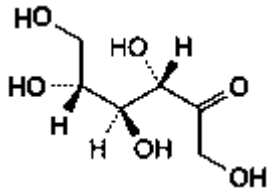
A. 4-*O*-β-D-galactopyranosyl-D-glucopyranose (lactose),



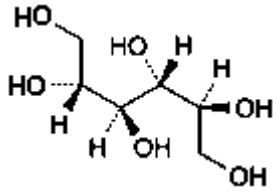
B. 6-*O*-β-D-galactopyranosyl-D-galactopyranose (1,6-galactosylgalactose),



C. D-galactopyranuronic acid (galacturonic acid),



D. D-tagatose,



E. galactitol (dulcitol).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

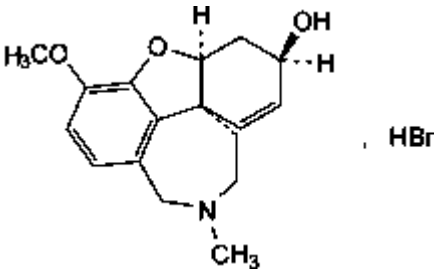
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Galantamine Hydrobromide

General Notices

(Ph. Eur. monograph 2366)



$C_{17}H_{22}BrNO_3$ 368.3 *1953-04-4*

Action and use

Cholinesterase inhibitor; treatment of Alzheimer's disease.

Preparations

Galantamine Oral Solution

Galantamine Prolonged-release Capsules

Galantamine Tablets

Ph Eur

DEFINITION

(4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-5,6,9,10,11,12-hexahydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide.

It is isolated from natural sources or produced by a synthetic process.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline or amorphous powder.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Sparingly soluble in water, very slightly soluble in anhydrous ethanol. It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *galantamine hydrobromide CRS*.

B. Specific optical rotation or enantiomeric purity (see Tests).

C. It gives reaction (a) of bromides (*2.3.1*).

TESTS

Solution S

Dissolve 0.60 g in *carbon dioxide-free water R* and dilute to 30.0 mL with the same solvent.

pH (*2.2.3*)

4.0 to 5.5 for solution S.

Specific optical rotation (*2.2.7*)

For galantamine from natural sources: -100 to -90 (dried substance), determined on solution S.

Enantiomeric purity

For galantamine produced by a synthetic process. Capillary electrophoresis (*2.2.47*). *Prepare the solutions immediately before use.*

Buffer electrolyte 8.9 g/L solution of *disodium hydrogen phosphate dihydrate R* adjusted to pH 3.0 with *phosphoric acid R*.

Test solution Dissolve 25.0 mg of the substance to be examined in 50.0 mL of *water R* and filter through a membrane filter (nominal pore size 0.22 µm).

Reference solution (a) Dissolve 5 mg of *galantamine racemic mixture CRS* in *water R* and dilute to 10 mL with the same solvent. Dilute 1 mL of the solution to 100 mL with *water R* and filter through a membrane filter (nominal pore size 0.22 µm).

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R* and filter through a membrane filter (nominal pore size 0.22 µm).

Blank solution Filter *water R* through a membrane filter (nominal pore size 0.22 µm).

Capillary:

— *material*: uncoated fused silica;

— *size*: effective length = about 0.50 m, Ø = 75 µm.

Temperature 20 °C.

www.webofpharma.com

https://thuocngocanh.com/

CZE buffer Dissolve 0.196 g of *α-cyclodextrin R* in 10.0 mL of buffer electrolyte and filter through a membrane filter (nominal pore size 0.22 µm).

Detection Spectrophotometer at 214 nm.

Preconditioning of the capillary At 137.9 kPa, rinse the capillary for 5 min with *water R* and for 5 min with CZE buffer.

Injection Under pressure (3.45 kPa) for 4 s.

Migration Apply a voltage of 15 kV.

Run time 35 min.

Relative migration times With reference to galantamine (migration time = about 18 min): impurity F = about 1.05.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to galantamine and impurity F.

Limit:

— *impurity F*: not more than 1.5 times the area of the principal peak in the electropherogram obtained with reference solution (b) (0.15 per cent).

Related substances

Liquid chromatography (*2.2.29*).

A. Galantamine from natural sources

Solvent mixture Mobile phase B, mobile phase A (10:90 *V/V*).

Test solution Dissolve 12 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *galantamine natural for system suitability CRS* (containing impurities A and E) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: dissolve 3.15 g of *ammonium formate R* in 900 mL of *water for chromatography R*, adjust to pH 3.8 with *anhydrous formic acid R* and dilute to 1000 mL with *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	95	5
5 - 20	95 → 80	5 → 20
20 - 23	80 → 50	20 → 50
23 - 31	50 → 20	50 → 80
31 - 35	20	80

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 287 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *galantamine natural for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and E.

Relative retention With reference to galantamine (retention time = about 12 min): impurity E = about 0.8; impurity A = about 1.5.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity E and galantamine.

Limits:

— *impurity E*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

www.webofpharma.com

https://thuocngocanh.com/

B. Galantamine produced by a synthetic process

Solvent mixture Dilute 50 mL of *methanol R* to 1000 mL with *water R*.

Test solution Dissolve 0.10 g of the substance to be examined in 50.0 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.5 mg of *galantamine synthetic for system suitability CRS* (containing impurities C and D) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm);

— *temperature*: 55 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.79 g of *disodium hydrogen phosphate dihydrate R* and 2.46 g of *sodium dihydrogen phosphate R* in *water for chromatography R* and dilute to 1000 mL with the same solvent; to 950 mL of the solution add 50 mL of *methanol R1*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	100	0
6 - 20	100 → 95	0 → 5
20 - 35	95 → 85	5 → 15
35 - 50	85 → 80	15 → 20

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *galantamine synthetic for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C and D.

Relative retention With reference to galantamine (retention time = about 16 min): impurity C = about 0.8; impurity D = about 2.1.

www.webofpharma.com

https://thuocngocanh.com/

System suitability Reference solution (b):

— *resolution*: minimum 4.5 between the peaks due to impurity C and galantamine.

Limits:

— *impurities C, D*: for each impurity, not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 2.0 g.

ASSAY

Dissolve 0.275 g in 40 mL of *water R*. Add 40 mL of *ethanol (96 per cent) R*. Add 5 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.2.20). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 36.83 mg of $C_{17}H_{22}BrNO_3$.

LABELLING

The label states the origin of the substance:

— isolated from natural sources;

— produced by a synthetic process.

IMPURITIES

Test A for related substances

A, B, E.

Specified impurities *A, E.*

www.webofpharma.com

https://thuocngocanh.com/

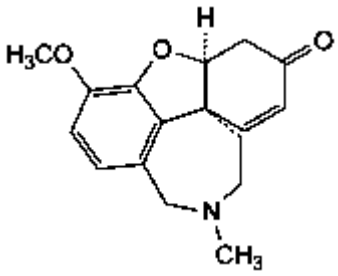
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B.*

Test B for related substances

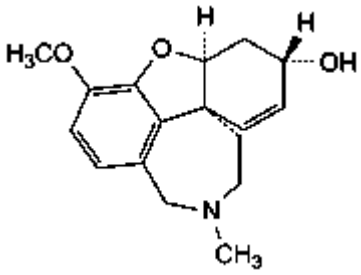
A, B, C, D, E, F.

Specified impurities *C, D, F.*

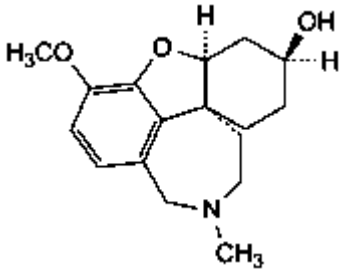
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, E.*



A. (4a*S*,8a*S*)-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepin-6-one (narwedine),



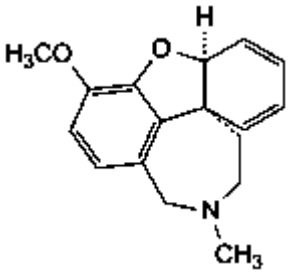
B. (4a*S*,6*S*,8a*S*)-3-methoxy-11-methyl-5,6,9,10,11,12-hexahydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol (*epi*-galantamine),



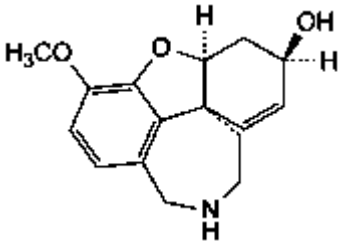
C. (4a*S*,6*S*,8a*R*)-3-methoxy-11-methyl-5,6,7,8,9,10,11,12-octahydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol (dihydrogalantamine),

www.webofpharma.com

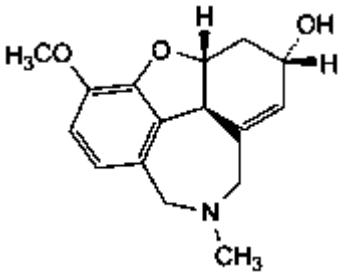
https://thuocngocanh.com/



D. (4a*S*,8a*S*)-3-methoxy-11-methyl-9,10,11,12-tetrahydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepine (anhydrogalantamine),



E. (4aS,6*R*,8a*S*)-3-methoxy-5,6,9,10,11,12-hexahydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol (*N*-demethylgalantamine),



F. (4a*R*,6*S*,8a*R*)-3-methoxy-11-methyl-5,6,9,10,11,12-hexahydro-4a*H*-[1]benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol (*ent*-galantamine).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Galantamine Oral Solution

General Notices

Action and use

Cholinesterase inhibitor; treatment of Alzheimer's disease.

DEFINITION

Galantamine Oral Solution is a solution containing Galantamine Hydrobromide in a suitable aqueous vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of galantamine, $C_{17}H_{21}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a volume of the oral solution containing the equivalent of 2 mg of galantamine, add 10 mL of *acetonitrile*, centrifuge and use the supernatant liquid.

(2) 0.026% w/v of *galantamine hydrobromide BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air and spray with *potassium iodobismuthate solution*, then immediately with *hydrogen peroxide solution (3 per cent)*. Examine the plate in white light.

MOBILE PHASE

1 volume of *glacial acetic acid*, 4 volumes of *butan-1-ol* and 5 volumes of *water*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acidity

pH, 4.0 to 6.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol* (50%).

(1) Dilute a volume of the oral solution containing the equivalent of 0.1 g of galantamine to 100 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.05% w/v of *galantamine natural for system suitability EPCRS*.

(4) 0.05% w/v of *galantamine synthetic for system suitability EPCRS*.

(5) 0.1% w/v of *galantamine hydrobromide impurity standard BPCRS*.

(6) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (3.5 µm) (Waters XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 55°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *methanol* and 95 volumes of a solution containing 0.079% w/v of *disodium hydrogen orthophosphate dihydrate* and 0.246% w/v of *sodium dihydrogen orthophosphate*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-6	100	0	isocratic
6-20	100→95	0→5	linear gradient
20-35	95→85	5→15	linear gradient
35-50	85→80	15→20	linear gradient
50-51	80→100	20→0	linear gradient
51-60	100	0	re-equilibration

www.webofpharma.com

https://thuocngocanh.com/

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to galantamine (retention time about 18 minutes) are: impurity E, about 0.3; impurity 2, about 0.4; impurity 1, about 0.6; impurity C, about 0.8; impurity B, about 1.1; impurity A, about 1.5 and impurity D, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and galantamine is at least 4.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to:

impurities A and E using the chromatogram obtained with solution (3) and the chromatogram supplied with *galantamine natural for system suitability EPCRS*;

impurities C and D using the chromatogram obtained with solution (4) and the chromatogram supplied with *galantamine synthetic for system suitability EPCRS*;

impurities B, 1, and 2 using the chromatogram obtained with solution (5) and the chromatogram supplied with *galantamine hydrobromide impurity standard BPCRS*.

Multiply the area of any peak corresponding to impurity A by a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to impurity B, C, D, 1, or 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.4% w/v *potassium dihydrogen orthophosphate*, adjusted to pH 6.5 with 5M *sodium hydroxide*.

(1) To a weighed quantity of the oral solution containing the equivalent of 25 mg of galantamine add 10 mL of *methanol*, and add sufficient of solution A to produce 50 mL. Dilute 1 volume of this solution to 10 volumes with solution A.

www.webofpharma.com

https://thuocngocanh.com/

(2) Dissolve 16 mg of *galantamine hydrobromide BPCRS* in 5 mL of *methanol*, and dilute to 25 mL with solution A. Dilute 1 mL of the resulting solution to 10 volumes with solution A.

(3) 0.05% w/v of *galantamine synthetic for system suitability EPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (3.5 µm) (Waters XTerra MS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 55°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of a solution containing 0.079% w/v of *disodium hydrogen orthophosphate dihydrate* and 0.246% w/v of *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and galantamine is at least 4.5.

DETERMINATION OF CONTENT

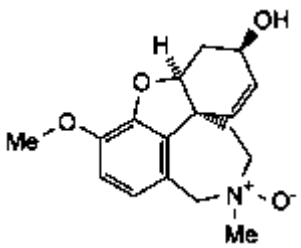
Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{17}H_{21}NO_3$, in the oral solution using the declared content of $C_{17}H_{21}NO_3$ in *galantamine hydrobromide BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of galantamine.

IMPURITIES

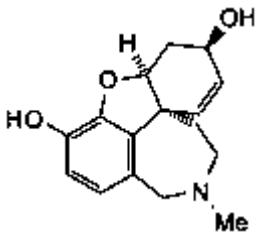
The impurities limited by the requirements of this monograph include impurities A to E listed under *Galantamine Hydrobromide* and:



1. galantamine-*N*-oxide

www.webofpharma.com

https://thuocngocanh.com/



2. *O*-demethylgalantamine

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Galantamine Prolonged-release Capsules

General Notices

Galantamine Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Cholinesterase inhibitor; treatment of Alzheimer's disease.

DEFINITION

Galantamine Prolonged-release Capsules contain Galantamine Hydrobromide. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of galantamine. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of galantamine, $C_{17}H_{21}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the powdered capsule contents containing the equivalent of 4 mg of galantamine, add 10 mL of *acetonitrile* and mix with the aid of ultrasound for 45 minutes. Centrifuge and use the supernatant liquid.

(2) 0.05% w/v of *galantamine hydrobromide BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air and spray with *potassium iodobismuthate solution*, then immediately with *hydrogen peroxide solution (3 per cent)*. Examine the plate in white light.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

1 volume of *glacial acetic acid*, 4 volumes of *butan-1-ol* and 5 volumes of *water*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in *methanol* (50%).

For capsules containing less than 24 mg of galantamine

(1) To 5 whole capsules add a quantity of *acetonitrile* that is equivalent to 20% of the volume of the flask and stir for 30 minutes. Add a quantity of *methanol* equivalent to 30% of the volume of the flask and stir for a further 30 minutes. Add a quantity of 1M *sodium hydroxide* equivalent to 5% of the volume of the flask and mix with the aid of ultrasound. Dilute with *methanol* to produce a solution containing the equivalent of 0.08% w/v of galantamine and filter (a 0.70-µm glass filter is suitable).

For capsules containing 24 mg or more of galantamine

(1) To 7 whole capsules add a quantity of *acetonitrile* equivalent to 20% of the volume of the flask and stir for 30 minutes. Add a quantity of *methanol* equivalent to 30% of the volume of the flask and stir for a further 30 minutes. Add a quantity of 1M *sodium hydroxide* equivalent to 5% of the volume of the flask and mix with the aid of ultrasound. Dilute with *methanol* to produce a solution containing the equivalent of 0.08% w/v of galantamine and filter (a 0.70-µm glass filter is suitable).

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.05% w/v of *galantamine natural for system suitability EPCRS*.

(4) 0.05% w/v of *galantamine synthetic for system suitability EPCRS*.

(5) 0.1% w/v of *galantamine hydrobromide impurity standard BPCRS*.

(6) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (3.5 µm) (Waters XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 55°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase A 5 volumes of *methanol* and 95 volumes of a solution containing 0.079% w/v of *disodium hydrogen orthophosphate dihydrate* and 0.246% w/v of *sodium dihydrogen orthophosphate*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-6	100	0	isocratic
6-20	100→95	0→5	linear gradient
20-35	95→85	5→15	linear gradient
35-50	85→80	15→20	linear gradient
50-51	80→100	20→0	linear gradient
51-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to galantamine (retention time about 18 minutes) are: impurity E, about 0.3; impurity 2, about 0.4; impurity 1, about 0.6; impurity C, about 0.8; impurity B, about 1.1; impurity A, about 1.5 and impurity D, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and galantamine is at least 4.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to:

impurities A and E using the chromatogram obtained with solution (3) and the chromatogram supplied with *galantamine natural for system suitability EPCRS*;

impurities C and D using the chromatogram obtained with solution (4) and the chromatogram supplied with *galantamine synthetic for system suitability EPCRS*;

impurities B, 1, and 2 using the chromatogram obtained with solution (5) and the chromatogram supplied with *galantamine hydrobromide impurity standard BPCRS*.

Multiply the area of any peak corresponding to impurity A by a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%);

the area of any peak corresponding to impurity E is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity B or impurity 2 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any peak corresponding to impurity C or impurity D is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.4% w/v *potassium dihydrogen orthophosphate*, adjusted to pH 6.5 with 5M *sodium hydroxide*.

For capsules containing less than 24 mg of galantamine

(1) To 5 whole capsules add a quantity of *acetonitrile* that is equivalent to 20% of the volume of the flask and stir for 30 minutes. Add a quantity of *methanol* equivalent to 30% of the volume of the flask and stir for a further 30 minutes. Add a quantity of 1M *sodium hydroxide* equivalent to 5% of the volume of the flask and mix with the aid of ultrasound. Dilute with *methanol* to produce a solution containing the equivalent of 0.08% w/v of galantamine and filter (a 0.70-µm glass filter is suitable). Dilute 1 volume of the filtrate to 10 volumes with *methanol (50%)*.

For capsules containing 24 mg or more of galantamine

(1) To 7 whole capsules add a quantity of *acetonitrile* equivalent to 20% of the volume of the flask and stir for 30 minutes. Add a quantity of *methanol* equivalent to 30% of the volume of the flask and stir for a further 30 minutes. Add a quantity of 1M *sodium hydroxide* equivalent to 5% of the volume of the flask and mix with the aid of ultrasound. Dilute with *methanol* to produce a solution containing the equivalent of 0.08% w/v of galantamine and filter (a 0.70-µm glass filter is suitable). Dilute 1 volume of the filtrate to 10 volumes with *methanol (50%)*.

(2) 0.1% w/v of *galantamine hydrobromide BPCRS* in solution A. Dilute 1 volume to 10 volumes with *methanol (50%)*.

(3) 0.05% w/v of *galantamine synthetic for system suitability EPCRS* in *methanol* (50%).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (3.5 µm) (Waters XTerra MS C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 55°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of a solution containing 0.079% w/v of *disodium hydrogen orthophosphate dihydrate* and 0.246% w/v of *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and galantamine is at least 4.5.

DETERMINATION OF CONTENT

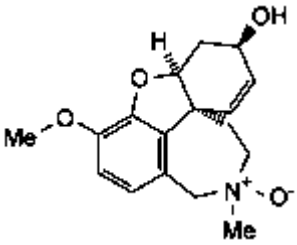
Calculate the content of $C_{17}H_{21}NO_3$ in the capsules using the declared content of $C_{17}H_{21}NO_3$ in *galantamine hydrobromide BPCRS*.

LABELLING

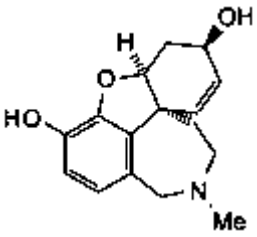
The quantity of active ingredient is stated in terms of the equivalent amount of galantamine.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A to E listed under *Galantamine Hydrobromide* and:



1. galantamine-*N*-oxide



2. *O*-demethylgalantamine

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Galantamine Tablets

General Notices

Action and use

Cholinesterase inhibitor; treatment of Alzheimer's disease.

DEFINITION

Galantamine Tablets contain Galantamine Hydrobromide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of galantamine, $C_{17}H_{21}NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of powdered tablets containing the equivalent of 4 mg of galantamine, add 10 mL of *acetonitrile* and mix with the aid of ultrasound for 45 minutes. Centrifuge and use the supernatant liquid.

(2) 0.05% w/v of *galantamine hydrobromide BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 8 cm.

(e) After removal of the plate, dry in air and spray with *potassium iodobismuthate solution*, then immediately with *hydrogen peroxide solution (3 per cent)*. Examine the plate in white light.

MOBILE PHASE

1 volume of *glacial acetic acid*, 4 volumes of *butan-1-ol* and 5 volumes of *water*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter and dilute with *water*, if necessary, to produce a solution containing the equivalent of 0.0008% w/v of galantamine. Measure the *absorbance* of this solution in a 5-cm cell, at 288 nm, Appendix II B, using *water* in the reference cell.

(2) 0.001% w/v of *galantamine hydrobromide BPCRS* in *water*. Measure the *absorbance* of this solution in a 5-cm cell, at 288 nm, Appendix II B, using *water* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of galantamine, $C_{17}H_{21}NO_3$, in the medium from the absorbances obtained and using the declared content of $C_{17}H_{21}NO_3$ in *galantamine hydrobromide BPCRS*.

LIMITS

The amount of galantamine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol* (50%).

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 0.1 g of galantamine with 50 mL. Dilute to 100 mL, mix and filter through a 0.45-µm nylon filter.

(2) Dilute 1 volume of solution (1) to 200 volumes.

(3) 0.05% w/v of *galantamine natural for system suitability EPCRS*.

(4) 0.05% w/v of *galantamine synthetic for system suitability EPCRS*.

(5) 0.1% w/v of *galantamine hydrobromide impurity standard BPCRS*.

(6) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (3.5 µm) (Waters XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 55°.

(e) Use a detection wavelength of 230 nm.

www.webofpharma.com

https://thuocngocanh.com/

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *methanol* and 95 volumes of a solution containing 0.079% w/v of *disodium hydrogen orthophosphate dihydrate* and 0.246% w/v of *sodium dihydrogen orthophosphate*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-6	100	0	isocratic
6-20	100→95	0→5	linear gradient
20-35	95→85	5→15	linear gradient
35-50	85→80	15→20	linear gradient
50-51	80→100	20→0	linear gradient
51-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to galantamine (retention time about 18 minutes) are: impurity E, about 0.3; impurity 2, about 0.4; impurity 1, about 0.6; impurity C, about 0.8; impurity B, about 1.1; impurity A, about 1.5 and impurity D, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and galantamine is at least 4.5.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to:

impurities A and E using the chromatogram obtained with solution (3) and the chromatogram supplied with *galantamine natural for system suitability EPCRS*;

impurities C and D using the chromatogram obtained with solution (4) and the chromatogram supplied with *galantamine synthetic for system suitability EPCRS*;

impurities B, 1, and 2 using the chromatogram obtained with solution (5) and the chromatogram supplied with *galantamine hydrobromide impurity standard BPCRS*.

Multiply the area of any peak corresponding to impurity A by a correction factor of 0.5.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 1.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.9%);

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity E is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%);

the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity C or impurity D is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4% of each);

the area of any peak corresponding to impurity 2 is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (6) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A 0.4% w/v *potassium dihydrogen orthophosphate*, adjusted to pH 6.5 with 5M *sodium hydroxide*.

(1) To 10 whole tablets add 50 mL of *methanol*, and mix with the aid of ultrasound for 15 minutes. Add 75 mL of solution A, and mix with the aid of ultrasound for 30 minutes with intermittent shaking. Allow to cool and dilute to 250 mL with solution A. Filter the resulting solution through a 0.45-µm nylon filter and dilute with solution A to produce a solution containing the equivalent of 0.0032% w/v of galantamine.
(2) Dissolve 16 mg of *galantamine hydrobromide BPCRS* in 5 mL of *methanol* and dilute to 25 mL with solution A. Dilute 1 volume of the resulting solution to 10 volumes with solution A.
(3) 0.05% w/v of *galantamine synthetic for system suitability EPCRS* in *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl amorphous organosilica polymer for chromatography* (3.5 µm) (Waters XTerra MS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 55°.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *methanol* and 95 volumes of a solution containing 0.079% w/v of *disodium hydrogen orthophosphate dihydrate* and 0.246% w/v of *sodium dihydrogen orthophosphate*.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity C and galantamine is at least 4.5.

DETERMINATION OF CONTENT

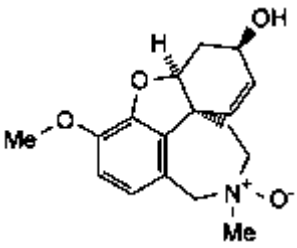
Calculate the content of $C_{17}H_{21}NO_3$ in the tablets using the declared content of $C_{17}H_{21}NO_3$ in *galantamine hydrobromide BPCRS*.

LABELLING

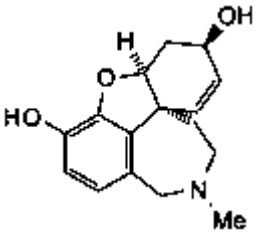
The quantity of active ingredient is stated in terms of the equivalent amount of galantamine.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A to E listed under *Galantamine Hydrobromide* and:



1. galantamine-*N*-oxide



2. *O*-demethylgalantamine

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

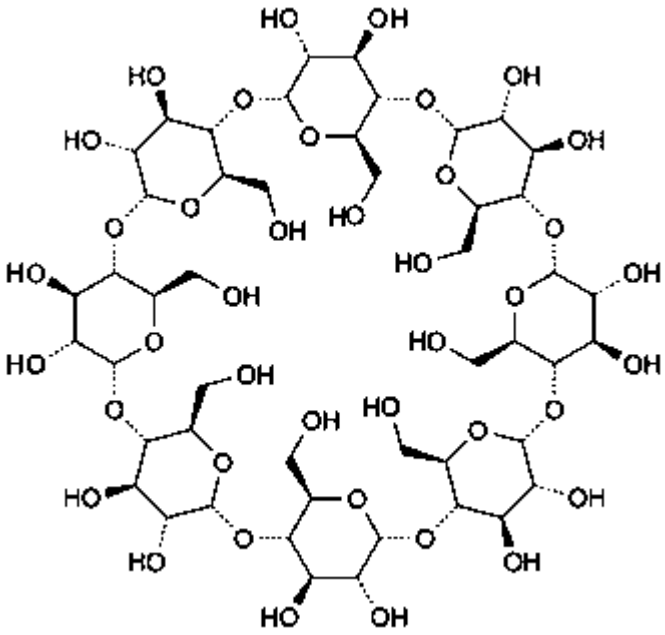
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gammadex

General Notices

(Ph. Eur. monograph 2769)



$[C_6H_{10}O_5]_8$ 1297 *17465-86-0*

Ph Eur

DEFINITION

Cyclooctakis-(1→4)-(α-D-glucopyranosyl) (cyclomaltooctaose or γ-cyclodextrin).

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, amorphous or crystalline, hygroscopic powder.

Solubility

Freely soluble in water, very slightly soluble in propylene glycol, practically insoluble in anhydrous ethanol and in methylene chloride. When dissolved in water, it forms a colloidal dispersion over time.

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *gammacyclodextrin CRS*.

TESTS

Solution S

Dissolve 1.000 g in *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

pH (2.2.3)

5.0 to 8.0.

Mix 1 mL of a 223.6 g/L solution of *potassium chloride R* and 30 mL of solution S.

Specific optical rotation (2.2.7)

+ 174 to + 180 (dried substance), determined on solution S after filtration through a membrane filter (nominal pore size 0.45 µm).

Reducing sugars

Maximum 0.2 per cent.

Test solution To 1 mL of solution S add 1 mL of *cupri-tartaric solution R4*. Heat on a water-bath for 10 min and allow to cool to room temperature. Add 10 mL of *ammonium molybdate reagent R1* and allow to stand for 15 min.

Reference solution Prepare at the same time and in the same manner as for the test solution, using 1 mL of a 0.02 g/L solution of *glucose R*.

Measure the absorbances (2.2.25) of the 2 solutions at the absorption maximum at 740 nm using *water R* as the compensation liquid. The absorbance of the test solution is not greater than that of the reference solution.

Light-absorbing impurities

Examine solution S after filtration through a membrane filter (nominal pore size 0.45 µm). The absorbance (2.2.25) is not greater than 0.10 between 230 nm and 350 nm and not greater than 0.05 between 350 nm and 750 nm.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.250 g of the substance to be examined in *water R* with heating, cool and dilute to 25.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Test solution (b) Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (a) Dissolve 25.0 mg of *alfadex CRS* (impurity A), 25.0 mg of *betadex CRS* (impurity B) and 25.0 mg of *gammacyclodextrin CRS* (gammadex) in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with *water R*.

Reference solution (c) Dissolve 25.0 mg of *gammacyclodextrin CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase *methanol R*, *water for chromatography R* (5:95 *V/V*).

Flow rate 1.5 mL/min.

Detection Differential refractometer maintained at a constant temperature (e.g. 35 °C).

Equilibration With the mobile phase for about 3 h.

Injection 50 µL of test solution (a) and reference solutions (a) and (b).

Run time 4 times the retention time of gammadex.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B.

Relative retention With reference to gammadex (retention time = about 7 min): impurity A = about 1.5; impurity B = about 3.2.

System suitability Reference solution (a):

— *resolution*: minimum 2.5 between the peaks due to gammadex and impurity A;

— *symmetry factor*: 0.8 to 1.8 for the peak due to gammadex.

Calculation of percentage contents:

— for impurities A and B, use the concentration of the corresponding impurity in reference solution (b);

— for impurities other than A and B, use the concentration of gammadex in reference solution (b).

Limits:

— *impurities A, B*: for each impurity, maximum 0.5 per cent;

— *sum of impurities other than A and B*: maximum 0.5 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *reporting threshold*: 0.15 per cent.

Loss on drying (*2.2.32*)

Maximum 11.0 per cent, determined on 1.000 g by drying in an oven at 120 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (c).

System suitability Reference solution (c):

— *symmetry factor*: 0.8 to 1.8 for the peak due to gammadex;

— *repeatability*: maximum relative standard deviation of 2.0 per cent determined on 5 injections.

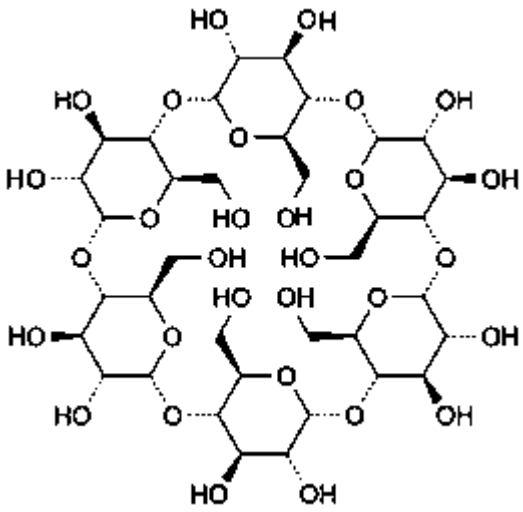
Calculate the percentage content of $[C_6H_{10}O_5]_8$ taking into account the assigned content of *gammacyclodextrin CRS*.

STORAGE

In an airtight container.

IMPURITIES

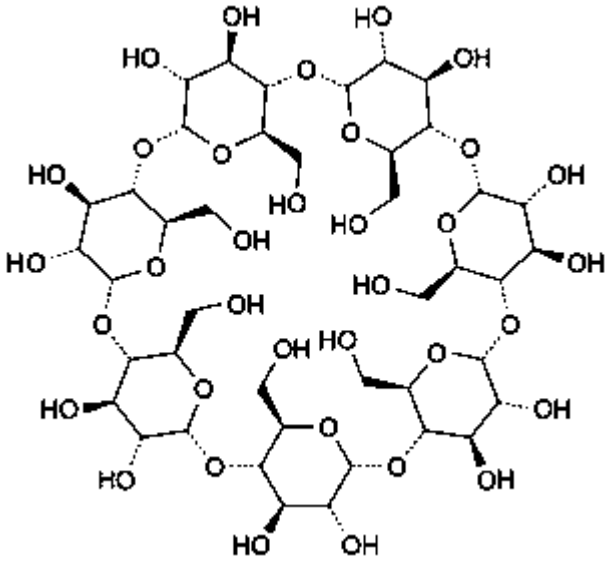
Specified impurities *A, B.*



A. cyclohexakis-(1→4)-(α-D-glucopyranosyl) (alfadex or cyclomaltohexaose or α-cyclodextrin),

www.webofpharma.com

https://thuvienthuocngocanh.com/



B. cycloheptakis-(1→4)-(α-D-glucopyranosyl) (betadex or cyclomaltoheptaose or β-cyclodextrin).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

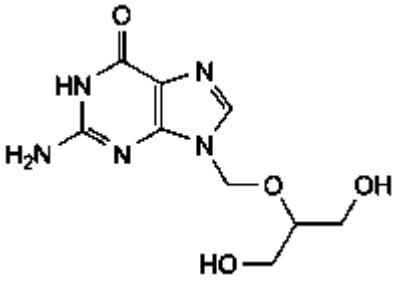
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Ganciclovir

General Notices

(Ph. Eur. monograph 1752)



$C_9H_{13}N_5O_4$ 255.2 *82410-32-0*

Action and use

Antiviral (cytomegalovirus).

Ph Eur

DEFINITION

2-Amino-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6*H*-purin-6-one.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Slightly soluble in water, very slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of mineral acids and alkali hydroxides.

It shows polymorphism (*5.9*).

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

Infrared absorption spectrophotometry (2.2.24).

Comparison *ganciclovir CRS*.

If the spectra obtained in the solid state show differences, dissolve 0.10 g of the substance to be examined and the reference substance separately in about 3.6 mL of *water R* at 80 °C. Allow to cool in an ice-bath and filter the precipitate. Dry in an oven at 105 °C for 3 h and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, *Method II*).

Dissolve 1.25 g in a 40 g/L solution of *sodium hydroxide R* and dilute to 25 mL with the same solution.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 30 mg of the substance to be examined in the mobile phase with the aid of ultrasound and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 3 mg of *ganciclovir CRS* in the mobile phase with the aid of ultrasound and dilute to 5.0 mL with the mobile phase.

Reference solution (c) Dissolve the contents of a vial of *ganciclovir impurity mixture CRS* (impurities A, B, C, D, E and F) in 1.0 mL of reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *strong cation-exchange silica gel for chromatography R* (10 µm);

— *temperature*: 40 °C.

Mobile phase Mix equal volumes of *acetonitrile R* and a 0.05 per cent *V*/*V* solution of *trifluoroacetic acid R*.

Flow rate 1.5 mL/min.

Detection Spectophotometer at 254 nm.

Injection 20 µL.

Run time 2.5 times the retention time of ganciclovir.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *ganciclovir impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention With reference to ganciclovir (retention time = about 14 min): impurity A = about 0.6; impurity B = about 0.67; impurity C = about 0.71; impurity D = about 0.8; impurity E = about 0.9; impurity F = about 2.0.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ganciclovir.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.3; impurity F = 0.7;

— *impurity F*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurities A, C, D, E*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.300 g.

Use *methanol R* as solvent. The substance to be examined has limited solubility in methanol. The sample will appear as a slurry. Replace the solvent after each titration.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.84 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

www.webofpharma.com

https://thuocngocanh.com/

ASSAY

Dissolve 0.200 g in 10 mL of *anhydrous formic acid R* and dilute to 60 mL with *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.52 mg of $C_9H_{13}N_5O_4$.

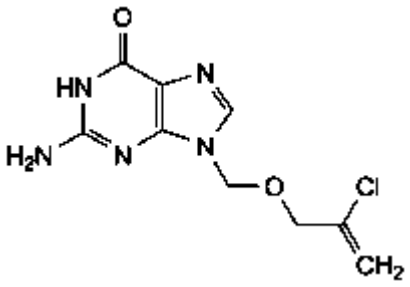
STORAGE

In an airtight container.

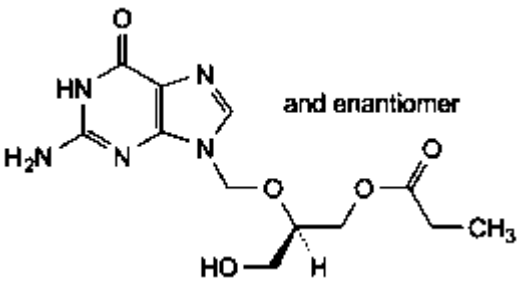
IMPURITIES

Specified impurities *A, B, C, D, E, F.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *H, I, J.*



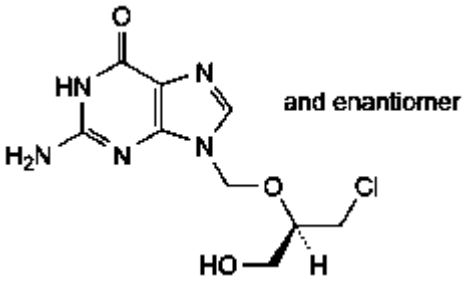
A. 2-amino-9-[[(2-chloroprop-2-en-1-yl)oxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



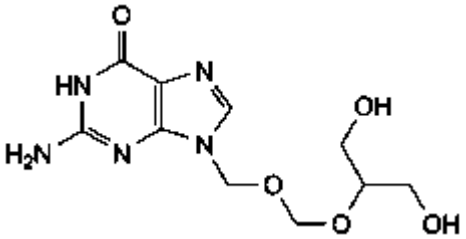
B. (2*RS*)-2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl propionate,

www.webofpharma.com

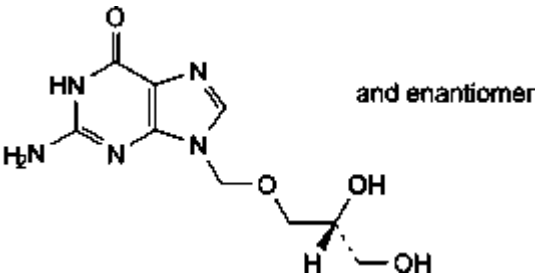
https://thuocngocanh.com/



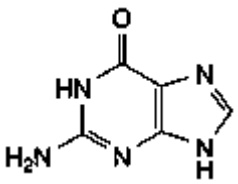
C. 2-amino-9-[[(1*RS*)-2-chloro-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



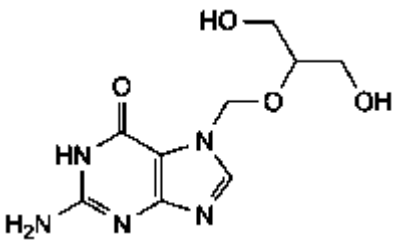
D. 2-amino-9-[[[2-hydroxy-1-(hydroxymethyl)ethoxy]methoxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



E. 2-amino-9-[[(2*RS*)-2,3-dihydroxypropoxy]methyl]-1,9-dihydro-6*H*-purin-6-one,



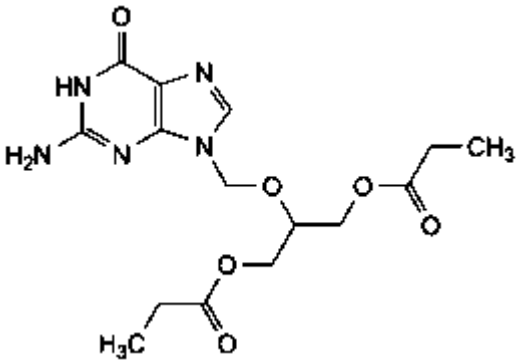
F. 2-amino-1,9-dihydro-6*H*-purin-6-one (guanine),



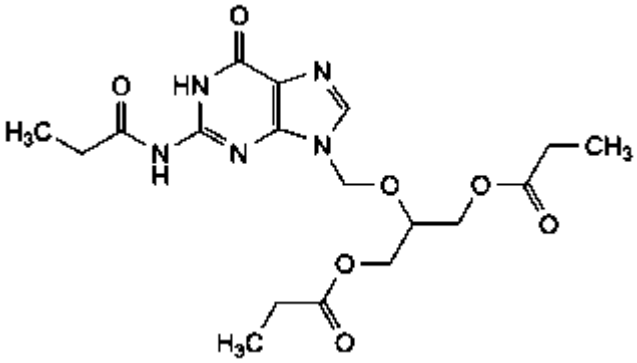
H. 2-amino-7-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-1,7-dihydro-6*H*-purin-6-one,

www.webofpharma.com

https://thuocngocanh.com/



I. 2-[(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]propane-1,3-diyl dipropanoate,



J. 2-[2-(propanoylamino)-6-oxo-1,6-dihydro-9*H*-purin-9-yl]methoxy]propane-1,3-diyl dipropanoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Acamprosate Gastro-resistant Tablets

General Notices

Gastro-resistant Acamprosate Tablets

Action and use

Treatment of alcoholism.

DEFINITION

Acamprosate Gastro-resistant Tablets contain Acamprosate Calcium. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of acamprosate calcium, $C_{10}H_{20}CaN_2O_8S_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

B. The powdered tablets yield reaction A characteristic of *calcium salts*, Appendix VI.

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

First stage

(a) Use Apparatus 1, rotating the basket at 180 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 2 hours, withdraw a 20-mL sample of the medium, filter through a 0.45-µm filter and dilute, if necessary, to produce a solution expected to contain 0.037% w/v of Acamprosate Calcium.

(2) 0.00185% w/v of *acamprosate calcium BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm x 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Synergi Hydro RP is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

To 850 mL of a solution containing 140.5 mg of *sodium perchlorate* and 170.95 mg of *tetrabutylammonium perchlorate* add 100 mL of *methanol R2* and dilute to 1000 mL with *water*.

DETERMINATION OF CONTENT

Calculate the total content of $C_{10}H_{20}CaN_2O_8S_2$ in the medium using the declared content of $C_{10}H_{20}CaN_2O_8S_2$in *acamprosate calcium BPCRS*.

LIMITS

The amount of Acamprosate Calcium released is not more than 5% of the stated amount.

Final stage

Buffer pH 6.8 Add 150 mL of 2M *sodium hydroxide* in sufficient 0.1M *citric acid* to produce 1000 mL, adjust the pH to 6.8, if necessary, with 0.5M *citric acid*.

(a) Use Apparatus 1, rotating the basket at 180 revolutions per minute.

(b) Replace the 0.1M *hydrochloric acid* in the vessel with 900 mL of buffer pH 6.8, previously held and maintained at 37°.

PROCEDURE

(1) After 2 hours, withdraw a 20-mL sample of the medium, filter through a 0.45-µm filter and dilute, if necessary, to produce a solution expected to contain 0.037% w/v of Acamprosate Calcium.

(2) 0.037% w/v of *acamprosate calcium BPCRS* in buffer pH 6.8.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{10}H_{20}CaN_2O_8S_2$ in the medium using the declared content of $C_{10}H_{20}CaN_2O_8S_2$in *acamprosate calcium BPCRS*.

LIMITS

The amount of Acamprosate Calcium released is not less than 75% (Q) of the stated amount.

Impurity A (homotaurine)

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Remove the tablet coating from 5 tablets by stirring with three 50-mL quantities of *acetone*. Allow the cores to dry at room temperature. Stir a quantity of the powdered tablets containing 333 mg of Acamprosate Calcium with 50 mL of *borate buffer solution pH 10.4* for 10 minutes and filter through a 0.45-µm filter. Dilute 3 mL of this solution to 20 mL with *borate buffer solution pH 10.4*. Place 3.0 mL of the solution obtained in a 25-mL ground-glass-stoppered tube. Add 0.15 mL of a freshly prepared 0.5% w/v solution of *fluorescamine* in *acetonitrile*. Shake immediately and vigorously for 30 seconds. Place in a water-bath at 50° for 30 min. Cool under a stream of cold water. Filter the supernatant liquid through a suitable filter.

(2) Dissolve 10 mg of *acamprosate impurity A EPCRS* in *borate buffer solution pH 10.4* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL *with* *borate buffer solution pH 10.4*. Treat 3.0 mL of this solution in the same way as solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) with a stainless steel pre-column (7.5 cm × 4.6 mm) both packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 261 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 6 times the retention time of impurity A.

MOBILE PHASE

10 volumes of *acetonitrile*, 10 mL of *methanol* and 80 volumes of *0.1M phosphate buffer solution pH 6.5*.

When the chromatograms are recorded under the prescribed conditions the retention time of fluorescamine is about 4 minutes and impurity A is about 8 minutes. Acamprosate is not detected.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Weigh and powder 20 tablets. Shake, with the aid of ultrasound, a quantity of the powdered tablets containing 333 mg of Acamprosate Calcium with 150 mL of mobile phase, dilute to 200 mL and filter through a 0.45-µm filter. Dilute 1 volume of the resulting solution to 5 volumes.

(2) 0.033% w/v of *acamprosate calcium BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (10 cm × 4.6 mm) with a stainless steel pre-column (7.5 cm × 4.6 mm) both packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS2 is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 205 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

To 850 mL of a solution containing 140.5 mg of *sodium perchlorate* and 342 mg of *tetrabutylammonium perchlorate* add 100 mL of *methanol R2* and dilute to 1000 mL with *water*.

SYSTEM SUITABILITY

Inject solution (2) five times. The test is not valid unless the relative standard deviation of the area of the principal peak is at most 2.0%.

DETERMINATION OF CONTENT

Calculate the content of $C_{10}H_{20}CaN_2O_8S_2$ in the tablets from the chromatogram obtained and using the declared content of $C_{10}H_{20}CaN_2O_8S_2$ in *acamprosate calcium BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Bisacodyl Gastro-resistant Tablets

General Notices

Bisacodyl Tablets

Gastro-resistant Bisacodyl Tablets

Action and use

Stimulant laxative.

DEFINITION

Bisacodyl Gastro-resistant Tablets contain Bisacodyl. They are made gastro-resistant by enteric coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of bisacodyl, $C_{22}H_{19}NO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

B. Extract a quantity of the powdered tablets containing 50 mg of Bisacodyl with 20 mL of *dichloromethane*, filter, evaporate the filtrate to dryness and dissolve the residue in 10 mL of a 0.5% v/v solution of *sulfuric acid*. To 2 mL of the solution obtained add *sulfuric acid*. A reddish violet colour is produced on addition of the concentrated acid.

C. Boil 2 mL of the solution obtained in test B with a little *nitric acid*; a yellow colour is produced. Cool and add 5M *sodium hydroxide*; the colour becomes yellowish brown.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

First stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 500 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 2 hours, withdraw a 10-mL sample of the medium.

(2) Dissolve 50 mg of *bisacodyl BPCRS* in 50 mL of *methanol* containing a drop of *orthophosphoric acid*. Dilute with *0.1M hydrochloric acid* to produce a solution containing 0.00005% w/v of *bisacodyl BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.8 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 230 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

350 volumes of a 0.1% w/v solution of *ammonium acetate*, adjusted to pH 8.0 with *dilute ammonia solution* and 650 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of $C_{22}H_{19}NO_4$ in the medium using the declared content of $C_{22}H_{19}NO_4$ in *bisacodyl BPCRS*.

LIMITS

The amount of bisacodyl released is not more than 5% of the stated amount.

After completion of the first stage, remove the basket from the vessel and dip once into a 100-mL beaker containing 80 mL of *water*. After the water has drained from the basket, transfer the tablet to Apparatus 2 and carry out the procedure described under Final stage.

Final stage

Solution A: Dissolve 8.9 g of *disodium hydrogen orthophosphate* and 10 g of *sodium lauryl sulfate* in 800 mL of *water*. Adjust to pH 7.5 with 0.1M *hydrochloric acid* and dilute to 1000 mL with *water*.

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 60 minutes, withdraw a 10-mL sample of the medium and filter through a 0.45-µm filter, discarding the first 3 mL. Use the filtered medium, diluted with dissolution medium, if necessary, to produce a solution expected to contain 0.00056% w/v of bisacodyl.

(2) Dissolve 50 mg of *bisacodyl BPCRS* in 50 mL of *methanol* containing a drop of *orthophosphoric acid*. Dilute with solution A to produce a solution containing 0.00056% w/v of *bisacodyl BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution – First stage may be used.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of $C_{22}H_{19}NO_4$ in the medium using the declared content of $C_{22}H_{19}NO_4$ in *bisacodyl BPCRS*.

LIMITS

The amount of bisacodyl released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B: A mixture of 4 volumes of *glacial acetic acid*, 30 volumes of *acetonitrile* and 66 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing 25 mg of Bisacodyl with 40 mL of solution B, dilute to 50 mL with solution B and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution B.

(3) Dissolve the contents of a vial of *bisacodyl for system suitability A EPCRS* in 1 mL of *acetonitrile* and mix with 1 mL of solution B.

(4) Dissolve 5 mg of *bisacodyl for peak identification EPCRS* in 2.5 mL of *acetonitrile* and dilute to 5 mL with solution B.

(5) Dilute 1 volume of solution (2) to 10 volumes with solution B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Waters Symmetry C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 265 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3.5 times the retention time of the principal peak.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of 0.025M *ammonium formate* previously adjusted to pH 5.0 with *anhydrous formic acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to bisacodyl (retention time about 13 minutes) are: impurity A, about 0.2; impurity B, about 0.4; impurity C, about 0.45; impurity E, about 0.9; impurity F, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.5, where H_p is the height above the baseline of the peak due to impurity E and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bisacodyl.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

identify any peak corresponding to impurity A using solution (3) and multiply the area of this peak by a correction factor of 0.7;

the area of any peak corresponding to impurity C is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

the area of any peak corresponding to impurity E is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity F is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution B: A mixture of 4 volumes of *glacial acetic acid*, 30 volumes of *acetonitrile* and 66 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing 10 mg of Bisacodyl with 40 mL of solution B, dilute to 50 mL and filter. Further dilute 1 volume to 4 volumes with solution B.
(2) 0.005% w/v of *bisacodyl BPCRS* in solution B.
(3) Dissolve the contents of a vial of *bisacodyl for system suitability A EPCRS* in 1 mL of *acetonitrile* and mix with 1 mL of solution B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used, with the exception of run time.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.5, where H_p is the height above the baseline of the peak due to impurity E and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to bisacodyl.

DETERMINATION OF CONTENT

Calculate the total content of bisacodyl, $C_{22}H_{19}NO_4$, in the tablets using the chromatograms obtained and the declared content of $C_{22}H_{19}NO_4$ in *bisacodyl BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Bisacodyl.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Diclofenac Gastro-resistant Tablets

General Notices

Diclofenac Tablets

Gastro-resistant Diclofenac Tablets

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Diclofenac Gastro-resistant Tablets contain Diclofenac Sodium. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of diclofenac sodium, $C_{14}H_{10}Cl_2NNaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Remove the coating from 10 tablets and powder the cores. Add 0.5 mL of *glacial acetic acid* and 15 mL of *methanol* to a quantity of the powdered tablet cores containing 0.15 g of Diclofenac Sodium and mix with the aid of ultrasound. Shake gently for 1 minute, filter and collect the filtrate in 15 mL of *water*. Filter the precipitate under reduced pressure (a Whatman GF/C filter paper is suitable), wash with four 5-mL quantities of *water* and dry at 105° for 2 to 3 hours. The *infrared absorption spectrum* of the dried precipitate, Appendix II A, is concordant with the *reference spectrum* of diclofenac *(RS 096)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 50 mg of Diclofenac Sodium with 70 mL of the mobile phase for 30 minutes, add sufficient of the mobile phase to produce 100 mL, mix, centrifuge an aliquot and filter the supernatant liquid through a 0.45-µm filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of this solution to 5 volumes with the mobile phase.
(3) 0.0005% w/v of *diclofenac sodium BPCRS* and 0.0005% w/v of *diclofenac impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack-pro C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 1.5 times the retention time of diclofenac.

MOBILE PHASE

34 volumes of a mixture of equal volumes of a 0.1% w/v solution of *orthophosphoric acid* and a 0.16% w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 66 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to diclofenac (retention time about 25 minutes) are: impurity A, about 0.4 and impurity F, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to diclofenac and diclofenac impurity A is at least 6.5.

LIMITS

Identify the peak due to impurity A using the chromatogram obtained with solution (3) and multiply the area of this peak by a correction factor of 0.7. Identify the peak due to impurity F using the relative retention time and multiply the area of this peak by a correction factor of 0.3.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 tablets with 700 mL of *methanol (50%)* for 30 minutes with the aid of ultrasound, add sufficient mobile phase to produce 1000 mL, centrifuge an aliquot and filter the supernatant liquid through a 0.45-µm filter. Dilute the filtrate with the mobile phase to produce a solution containing 0.005% w/v of Diclofenac Sodium.

(2) 0.005% w/v of *diclofenac sodium BPCRS* in the mobile phase.

(3) 0.0005% w/v of *diclofenac sodium BPCRS* and 0.0005% w/v of *diclofenac impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (end-capped Zorbax C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

20 volumes of a mixture of equal volumes of a 0.1% w/v solution of *orthophosphoric acid* and a 0.16% w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 80 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions, the retention times are about 5 minutes for diclofenac and about 4 minutes for diclofenac impurity A.

SYSTEM SUITABILITY

The Assay is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to diclofenac and diclofenac impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ in the tablets using the declared content of $C_{14}H_{10}Cl_2NNaO_2$ in *diclofenac sodium BPCRS*.

STORAGE

Diclofenac Gastro-resistant Tablets should be protected from moisture.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Diclofenac Sodium.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin Gastro-resistant Capsules

General Notices

Gastro-resistant Erythromycin Capsules

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin Gastro-resistant Capsules contain Erythromycin. They are manufactured using gastro-resistant capsule shells or prepared by filling capsules with granules or particles covered with a gastro-resistant coating.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)

90.0 to 110.0% of the stated amount of Erythromycin.

IDENTIFICATION

Shake a quantity of the mixed capsule contents containing 0.1 g of Erythromycin with 5 mL of *dichloromethane*, decolourise, if necessary, with *activated charcoal*, filter through a 0.45-µm PTFE filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, after drying *in vacuo* at 60° for 10 minutes, is concordant with the *reference spectrum* of erythromycin *(RS 123)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A A solution containing 0.68% w/v of *potassium dihydrogen orthophosphate* and 0.09% w/v of *sodium hydroxide* in water. Adjust the solution to pH 6.8, if necessary, using *orthophosphoric acid* or *sodium hydroxide*.

First stage

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of 0.06M *hydrochloric acid*, at a temperature of 37° as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

After 1 hour remove the basket from the dissolution medium, and immediately lower the basket into the second dissolution medium. Discard the first medium.

Final stage

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37° as the medium.

PROCEDURE

After 1 hour remove the basket from the dissolution medium. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, in solution A. *Prepare the solutions immediately before use and protect from light.*

(1) Withdraw a sample of the second medium and filter. Use the filtered medium, diluted with solution A, if necessary, to produce a solution expected to contain 0.028% w/v of Erythromycin.

(2) 0.028% w/v of *erythromycin BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under related substances may be used with isocratic elution using mobile phase A. Continue the chromatography for twice the retention time of erythromycin A.

When the chromatograms are recorded under the prescribed conditions, the retention time of erythromycin A is about 23 minutes.

DETERMINATION OF CONTENT

Calculate the content of erythromycin A, $C_{37}H_{67}NO_{13}$ in the medium using the declared content of $C_{37}H_{67}NO_{13}$ in *erythromycin BPCRS*.

The amount of erythromycin A released in the final stage is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B. *Prepare the solutions immediately before use and protect from light.*

Solution B 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Disperse a sufficient quantity of contents of the capsules in solution B and dilute to produce a solution containing 0.4% of w/v erythromycin and filter (0.45µm GF/C filter is suitable).

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

(4) 0.4% w/v of *erythromycin for impurity M identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

www.webofpharma.com

https://thuocngocanh.com/

(a) Use a stainless steel column (25 cm × 4.6) mm packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (X-Terra RP18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 65°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 35 volumes of *acetonitrile R1* and 60 volumes of *water*.

Mobile phase B 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 50 volumes of *acetonitrile R1* and 45 volumes of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-44	100	0	isocratic
44-46	100→0	0→100	linear gradient
46-61	0	100	isocratic
61-63	0→100	100→0	linear gradient
63-80	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to erythromycin A (retention time about 23 minutes) are: impurity H, about 0.3; impurity A, about 0.4; impurity B, about 0.5; erythromycin C, about 0.55; impurity M, about 0.58; impurity L, about 0.63; impurity C, about 0.9; impurity D, about 1.6; erythromycin B, about 1.75; impurity F, about 1.8 and impurity E, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

LIMITS

Identify any peaks corresponding to impurities D, E, F and L in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the corresponding correction factors: impurity D, 2.0; impurity E, 0.08;

www.webofpharma.com

https://thuocngocanh.com/

impurity F, 0.08; impurity L, 0.11.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity A or B is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (2% of each);

the area of any peak corresponding to impurity D, E, F, H or M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak corresponding to impurity L is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak*, other than the peaks due to erythromycin B and C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any *secondary peaks*, other than the peaks due to erythromycin B and C is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peak due to erythromycin B and erythromycin C and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%).

The content of each of erythromycin B and erythromycin C, as determined under Assay, is not more than 5%.

Water

The contents of the capsules contain not more than 7.5% w/w of water, Appendix IX C, using 10% w/v of *imidazole* in *methanol* in the titration vessel.

ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B. *Prepare the solutions immediately before use and protect from light.*

Solution B 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Disperse a quantity of the contents of the capsules by shaking with solution B and dilute to produce a solution containing 0.4% w/v Erythromycin and filter.

(2) 0.4% w/v of *erythromycin BPCRS*.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

DETERMINATION OF CONTENT

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatograms obtained with solutions (1) and (2) and the declared contents of $C_{37}H_{67}NO_{13}$, $C_{37}H_{67}NO_{12}$ and $C_{36}H_{65}NO_{13}$ respectively in *erythromycin BPCRS*.

STORAGE

Erythromycin Gastro-resistant Capsules should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Erythromycin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Erythromycin Gastro-resistant Tablets

General Notices

Erythromycin Tablets

Gastro-resistant Erythromycin Tablets

Action and use

Macrolide antibacterial.

DEFINITION

Erythromycin Gastro-resistant Tablets contain Erythromycin. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of erythromycins, calculated as the sum of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$)

90.0 to 110.0% of the stated amount of Erythromycin.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.1 g of Erythromycin with 5 mL of *dichloromethane*, decolourise, if necessary, with *activated charcoal*, filter through a 0.45-µm PTFE filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, after drying *in vacuo* at 60° for 10 minutes, is concordant with the *reference spectrum* of erythromycin *(RS 123)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Solution A A solution containing 0.68% w/v of *potassium dihydrogen orthophosphate* and 0.09% w/v of *sodium hydroxide* in water. Adjust the solution to pH 6.8, if necessary, using *orthophosphoric acid* or *sodium hydroxide*.

First stage

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of 0.06M *hydrochloric acid*, at a temperature of 37° as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

PROCEDURE

After 1 hour remove the basket from the dissolution medium, and immediately lower the basket into the second dissolution medium.

Final stage

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 50 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37º.

PROCEDURE

After 1 hour remove the basket from the dissolution medium. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, in solution A. *Prepare the solutions immediately before use and protect from light.*

(1) Withdraw a sample of the second medium and filter. Use the filtered medium, diluted with solution A, if necessary, to produce a solution expected to contain 0.028% w/v of erythromycin.

(2) 0.028% w/v of erythromycin BPCRS.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used with isocratic elution using mobile phase A. Continue the chromatography for twice the retention time of erythromycin A.

When the chromatograms are recorded under the prescribed conditions, the retention time of erythromycin A is about 23 minutes.

DETERMINATION OF CONTENT

Calculate the content of erythromycin A, $C_{37}H_{67}NO_{13}$, using the declared content of $C_{37}H_{67}NO_{13}$ in *erythromycin BPCRS*.

The amount of erythromycin A released in the final stage is not less than 75% of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B. *Prepare the solutions immediately before use and protect from light.*

Solution B 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Dissolve a quantity of powdered tablets in solution B and dilute to produce a solution containing 0.4% w/v erythromycin.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

(4) 0.4% w/v of *erythromycin for impurity M identification EPCRS*.

(5) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer* (3.5 µm) (X-Terra RP18 is suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 65°.

(e) Use a detection wavelength of 210 nm.

(f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 35 volumes of *acetonitrile R1* and 60 volumes of *water*.

Mobile phase B 5 volumes of a 3.5% w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 7.0 using *dilute phosphoric acid*, 50 volumes of *acetonitrile R1* and 45 volumes of *water*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-44	100	0	isocratic
44-46	100→0	0→100	linear gradient
46-61	0	100	isocratic
61-63	0→100	100→0	linear gradient
63-80	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to erythromycin A (retention time about 23 minutes) are: impurity H, about 0.3; impurity A, about 0.4; impurity B, about 0.5; erythromycin C, about 0.55; impurity M, about 0.58; impurity L, about 0.63; impurity C, about 0.9; impurity D, about 1.6; erythromycin B, about 1.75; impurity F, about 1.8 and impurity E, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

LIMITS

Identify any peaks corresponding to impurities D, E, F and L in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the corresponding correction factors: impurity D, 2.0; impurity E, 0.08; impurity F, 0.08; impurity L, 0.11.

www.webofpharma.com

https://thatuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the area of any peak corresponding to impurity A or B is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (2% of each);

the area of any peak corresponding to impurity D, E, F, H or M is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1% of each);

the area of any peak corresponding to impurity L is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak*, other than the peaks due to erythromycin B and C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the sum of the areas of any *secondary peaks*, other than the peaks due to erythromycin B and C is not greater than 7 times the principal peak in the chromatogram obtained with solution (2) (7%).

Disregard any peak due to erythromycin B and erythromycin C and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%).

The content of each of erythromycin B and erythromycin C, as determined under Assay, is not more than 5%.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solution B. *Prepare the solutions immediately before use and protect from light.*

Solution B 40 volumes of a 1.15% w/v solution of *dipotassium hydrogen orthophosphate* adjusted to pH 8.0 using *dilute phosphoric acid* and 60 volumes of *methanol*.

(1) Dissolve a quantity of the powdered tablets with solution B and dilute to produce a solution containing 0.4% w/v erythromycin.
(2) 0.4% w/v of *erythromycin BPCRS*.
(3) 0.4% w/v of *erythromycin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between the peaks due to impurity B and erythromycin C is at least 1.2;

the *peak-to-valley ratio* is at least 2.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin A;

www.webofpharma.com

https://thuocngocanh.com/

the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to impurity F and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to erythromycin B.

DETERMINATION OF CONTENT

Calculate the percentage content of erythromycin A ($C_{37}H_{67}NO_{13}$), erythromycin B ($C_{37}H_{67}NO_{12}$) and erythromycin C ($C_{36}H_{65}NO_{13}$) using the chromatograms obtained with solutions (1) and (2) and the declared contents of $C_{37}H_{67}NO_{13}$, $C_{37}H_{67}NO_{12}$ and $C_{36}H_{65}NO_{13}$ respectively in *erythromycin BPCRS*.

STORAGE

Erythromycin Gastro-resistant Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Erythromycin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Lansoprazole Gastro-resistant Capsules

General Notices

Gastro-resistant Lansoprazole Capsules

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Lansoprazole Gastro-resistant Capsules contain Lansoprazole. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of lansoprazole, $C_{16}H_{14}F_3N_3O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the finely powdered contents of the capsules containing 30 mg of Lansoprazole with 50 mL of *methanol*, filter and dilute 1 volume to 50 volumes. The *light absorption*, Appendix II B, in the range 220 nm to 350 nm exhibits a maximum at 284 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Mix 11 volumes of 0.25M *trisodium orthophosphate* and 22 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 100 volumes with *water* and adjust the pH, if necessary, to 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution A).

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution B).

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 150 revolutions per minute.

(b) Use as the media the solutions described sequentially below.

First stage (pH 4.5)

www.webofpharma.com

https://thuocngocanh.com/

Use as the medium 700 mL of *0.05M* *phosphate buffer solution pH 4.5*. After 45 minutes, withdraw 5 mL of the medium, filter, dilute to 25 mL with solution A and retain the samples for analysis as described below. Proceed immediately to the final stage.

Final stage (pH 6.8)

Within 5 minutes, add 200 mL of solution B at 37° to the vessel. Maintain the rotation speed at 150 revolutions per minute and continue to operate the apparatus for 45 minutes. Withdraw 5 mL of the medium, filter, dilute to 25 mL with solution A and retain the samples for analysis as described below.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the sample solutions taken above.

(2) Dissolve a sufficient quantity of *lansoprazole BPCRS* in solution A and dilute with sufficient *water* to produce a final solution of the same concentration as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{16}H_{14}F_3N_3O_2S$ in the medium using the declared content of $C_{16}H_{14}F_3N_3O_2S$ in *lansoprazole BPCRS*.

LIMITS

The amount of lansoprazole released after the first stage is not more than 10% of the stated amount. The amount of lansoprazole released after the final stage is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Mix 1 volume of *triethylamine* with 60 volumes of *water*, adjust the pH to 10.5 using *orthophosphoric acid*, add 40 volumes of *acetonitrile* and mix (solvent A).

(1) Shake a quantity of the finely powdered contents of the capsules containing 50 mg of Lansoprazole with 50 mL of solvent A and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A and dilute a further 1 volume to 5 volumes with solvent A.

(3) Dilute 1 volume of solution (2) to 4 volumes with solvent A.

(4) 0.1% w/v of *lansoprazole impurity standard BPCRS* in solvent A.

(5) 0.0004% w/v of *2-mercaptobenzimidazole* (impurity E) in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *amidohexadecylsilyl* *silica gel for chromatography* (5 µm) (Supelcosil LC-ABZ is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

www.webofpharma.com

https://thatuocngocanh.com/

(e) Use a detection wavelength of 285 nm.

(f) Inject 10 µL of each solution.

(g) Identify any peaks in the chromatogram obtained with solution (1) corresponding to lansoprazole impurities A and B using solution (3).

MOBILE PHASE

1 volume of *triethylamine*, 60 volumes of *water*, adjusted to pH 6.2 using *orthophosphoric acid* and 40 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to lansoprazole and impurity B is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity B is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.4%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not more than 2.0%.

Disregard any peak with an area less the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and protect from light.

Mix 1 volume of *triethylamine* with 60 volumes of *water*, adjust the pH to 10.5 using *orthophosphoric acid*, add 40 volumes of *acetonitrile* and mix (solvent A).

(1) Add a quantity of the finely powdered mixed contents of 20 capsules containing 20 mg of Lansoprazole to 100 mL of solvent A, shake for 30 minutes and filter.

(2) 0.02% w/v of *lansoprazole BPCRS*.

(3) 0.01% w/v of *lansoprazole impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to lansoprazole and impurity B is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{14}F_3N_3O_2S$ in the capsules using the declared content of $C_{16}H_{14}F_3N_3O_2S$ in *lansoprazole BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Lansoprazole Gastro-resistant Tablets

General Notices

Gastro-resistant Lansoprazole Tablets

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Lansoprazole Gastro-resistant Tablets contain Lansoprazole. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of lansoprazole, $C_{16}H_{14}F_3N_3O_2S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A Shake a quantity of the powdered tablets containing 30 mg of Lansoprazole with 50 mL of *methanol*, filter and dilute 1 volume to 50 volumes. The *light absorption*, Appendix II B, in the range 220 nm to 350 nm exhibits a maximum at 285 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Mix 11 volumes of 0.25M *trisodium orthophosphate* and 22 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 100 volumes with *water* and adjust the pH, if necessary, to 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution A).

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution B).

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 150 revolutions per minute.

(b) Use as the media the solutions described sequentially below.

First stage (pH 4.5)

www.webofpharma.com

https://thuocngocanh.com/

Use as the medium 700 mL of *0.05*M *phosphate buffer solution pH 4.5*. After 45 minutes, withdraw 5 mL of the medium, filter, dilute to 25 mL with solution A and retain the samples for analysis as described below. Proceed immediately to the final stage.

Final stage (pH 6.8)

Within 5 minutes, add 200 mL of solution B at 37° to the vessel. Maintain the rotation speed at 150 revolutions per minute and continue to operate the apparatus for 45 minutes. Withdraw 5 mL of the medium, filter, dilute to 25 mL with solution A and retain the samples for analysis as described below.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) The sample solutions taken above.
(2) Dissolve a sufficient quantity of *lansoprazole BPCRS* in solution A and dilute with sufficient *water* to produce a final solution of the same concentration as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{16}H_{14}F_3N_3O_2S$, in the medium using the declared content of $C_{16}H_{14}F_3N_3O_2S$ in *lansoprazole BPCRS*.

LIMITS

The amount of lansoprazole released after the first stage is not more than 10% of the stated amount. The amount of lansoprazole released after the final stage is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Mix 1 volume of *triethylamine* with 60 volumes of *water*, adjust the pH to 10.5 using *orthophosphoric acid*, add 40 volumes of *acetonitrile* and mix (solvent A).

(1) Shake a quantity of the powdered tablets containing 50 mg of Lansoprazole with 50 mL of solvent A and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A and dilute a further 1 volume to 5 volumes with solvent A.
(3) Dilute 1 volume of solution (2) to 4 volumes with solvent A.
(4) 0.1% w/v of *lansoprazole impurity standard BPCRS* in solvent A.
(5) 0.0003% w/v of *2-mercaptobenzimidazole* (impurity E) in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *amidohexadecylsilyl* *silica gel for chromatography* (5 µm) (Supelcosil LC-ABZ is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an ambient column temperature.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 285 nm.

(f) Inject 10 µL of each solution.

(g) Identify any peaks in the chromatogram obtained with solution (1) corresponding to lansoprazole impurities A and B using solution (3).

MOBILE PHASE

1 volume of *triethylamine*, 60 volumes of *water*, adjusted to pH 6.2 using *orthophosphoric acid* and mix the solution with 40 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to lansoprazole and impurity B is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peak corresponding to impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not more than 2.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in solvent A, protected from light.

Mix 1 volume of *triethylamine* with 60 volumes of *water*, adjust the pH to 10.5 using *orthophosphoric acid*, add 40 volumes of *acetonitrile* and mix (solvent A).

(1) To a quantity of the powdered tablets containing 50 mg of Lansoprazole add 50 mL of solvent A, shake for 30 minutes and filter. Dilute 1 volume to 5 volumes with solvent A.

(2) 0.02% w/v of *lansoprazole BPCRS*.

(3) 0.01% w/v of *lansoprazole impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to lansoprazole and impurity B is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of lansoprazole, $C_{16}H_{14}F_3N_3O_2S$, in the tablets using the declared content of $C_{16}H_{14}F_3N_3O_2S$ in *lansoprazole BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Mesalazine Gastro-resistant Tablets

General Notices

Gastro-resistant Mesalazine Tablets

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Mesalazine Gastro-resistant Tablets contain Mesalazine. They are made gastro-resistant by gastro-resistant coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of mesalazine, $C_7H_7NO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Mix a quantity of the powdered tablets containing 25 mg of Mesalazine in 15 mL of 0.01M *hydrochloric acid* for 50 minutes with the aid of ultrasound, with additional vortex mixing at 10 minute intervals; add sufficient 0.01M *hydrochloric acid* to produce 25 mL, mix and filter. To 1 volume of the filtrate add sufficient 0.01M *hydrochloric acid* to produce 50 volumes. The *light absorption*, Appendix II B, in the range 190 to 400 nm exhibits maxima at 302 nm and 232 nm and minima at 258 nm and 219 nm.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix for 10 minutes with the aid of ultrasound, a quantity of the powdered tablets containing 50 mg of Mesalazine in 30 mL of 0.01M *hydrochloric acid*, add sufficient 0.01M *hydrochloric acid* to produce 50 mL, mix using a vortex mixer and filter through a 0.45-µm membrane filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.01M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 10 volumes with 0.01M *hydrochloric acid*.

(3) 0.1% w/v of *mesalazine for system suitability EPCRS* in 0.01M *hydrochloric acid*.

(4) 0.0001% w/v each of *4-aminosalicylic acid* (impurity E), *2,5-dihydroxybenzoic acid* (impurity G), *2-chlorobenzoic acid* (impurity L), *2-chloro-5-nitrobenzoic acid* (impurity M), *5-nitrosalicylic acid* (impurity N), *sulfanilic acid* (impurity O), *3-nitrosalicylic acid* (impurity R) and

www.webofpharma.com

https://thuocngocanh.com/

0.0003% w/v of *salicylic acid* (impurity H) in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 240 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide*.

Mobile phase B 40 volumes of *acetonitrile* and 60 volumes of mobile phase A.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 20	100 → 85	0 → 15	linear gradient
20 - 40	85 → 25	15 → 75	linear gradient
40 - 60	25 → 0	75 → 100	linear gradient
60 - 61	0 → 100	100 → 0	linear gradient
61 - 70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 6 minutes) are: impurity O, about 0.55; impurity J, about 0.6; impurity E, about 0.8; impurity F, about 1.36; impurity G, about 1.4; impurity P, about 1.5; impurity L, about 2.0; impurity M, about 3.3; impurity H, about 3.5; impurity R, about 5.1 and impurity N, about 5.5.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to impurity F and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

Use the chromatogram supplied with *mesalazine for system suitability EPCRS* and the chromatogram obtained with solution (3) to identify any peaks due to impurities F, J and P and the chromatogram obtained with solution (4) to identify any peaks due to impurities E, G, H, L, M, N, O and R, in the chromatogram obtained in solution (1). Multiply the area of these peaks by the corresponding correction factors: impurity E, 1.3; impurity G, 1.4; impurity H, 1.4; impurity J, 2.0; impurity L, 4.5; impurity M, 1.7; impurity O, 0.6; impurity P, 0.6; impurity R, 1.3.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to salicylic acid is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity H is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E, F, G, J, L, M, P or R is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Impurities A and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions and freshly prepared mobile phases.

(1) Mix a quantity of the powdered tablets containing 50 mg of Mesalazine in 30 mL of mobile phase A for 10 minutes with the aid of ultrasound, add sufficient mobile phase A to produce 50 mL, mix using a vortex mixer and filter through a 0.45-µm membrane filter.
(2) Mix 1 volume of a 0.002% w/v solution of *4-aminophenol* (impurity A) in mobile phase A with 1 volume of 0.002% w/v of *2-aminophenol* (impurity C) in mobile phase A, add sufficient mobile phase A to produce 100 volumes and mix.
(3) To 1 volume of solution (1) add sufficient mobile phase A to produce 200 volumes, mix 1 volume of this solution with 1 volume of 0.0005% w/v *2-aminophenol* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

Mobile phase A 0.22% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* *in* *water*.

Mobile phase B 0.17% w/v of *perchloric acid* and 0.1% w/v of *orthophosphoric acid* in *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 - 8	100	0	isocratic
8 - 25	100 → 40	0 → 60	linear gradient
25 - 30	40 → 100	60 → 0	linear gradient
30 - 40	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to mesalazine (retention time about 9 minutes) are: impurity A, about 0.5 and impurity C, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A or impurity C is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (200 ppm of each).

Impurity K

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 2 mL of 0.01M *sodium hydroxide* and 5 drops of 1M *sodium hydroxide* to a quantity of the powdered tablets containing 50 mg of Mesalazine, add 15 mL of the mobile phase and mix for 20 minutes with the aid of ultrasound, add sufficient of the mobile phase to produce 25 mL and filter through a 0.45-µm membrane filter.

(2) 0.00000278% w/v of *aniline hydrochloride* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP18e is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 205 nm.

(f) Inject 50 µL of each solution.

www.webofpharma.com

https://thuocngocanh.com/

MOBILE PHASE

15 volumes of *methanol* and 85 volumes of a solution containing 0.141% w/v of *potassium dihydrogen orthophosphate* and 0.047% w/v of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 8.0 with 4.2% w/v *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the retention time of aniline is about 15 minutes.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to aniline (impurity K) is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (10 ppm).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 25 mg of Mesalazine in 15 mL of 0.1M *hydrochloric acid* for 50 minutes with the aid of ultrasound, with additional vortex mixing at 10 minute intervals; add sufficient 0.1M *hydrochloric acid* to produce 25 mL, mix and filter. To 1 volume of the filtrate add sufficient 0.1M *hydrochloric acid* to produce 50 volumes.
(2) 0.002% w/v of *mesalazine BPCRS* prepared by dissolving in 0.1M *hydrochloric acid* with the aid of ultrasound.
(3) Prepare a 0.01% w/v solution of *3-aminosalicylic acid* in 0.1M *hydrochloric acid* and dilute 1 volume of this solution to 100 volumes with a 0.1% w/v solution of *mesalazine BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl amorphous organosilica polymer* (5 µm) (XTerra MS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

A 0.69% w/v solution of *sodium dihydrogen orthophosphate monohydrate*, adjusted to pH 6.2 with *dilute sodium hydroxide solution*.

SYSTEM SUITABILITY

In the chromatogram obtained with solution (3) the *peak-to-valley ratio* is at least 3.0, where H_p is the height above the baseline of the peak due to 3-aminosalicylic acid and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

DETERMINATION OF CONTENT

Calculate the content of $C_7H_7NO_3$ in the tablets using the declared content of $C_7H_7NO_3$ in *mesalazine BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Mesalazine.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Naproxen Gastro-resistant Tablets

General Notices

Gastro-resistant Naproxen Tablets

Action and use

Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

DEFINITION

Naproxen Gastro-resistant Tablets contain Naproxen. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of naproxen, $C_{14}H_{14}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Remove the coating from a number of tablets and powder the uncoated cores. Extract a quantity of the powdered tablets containing 0.2 g of Naproxen with 20 mL of *methanol*, shake for 15 minutes, filter, evaporate the filtrate and dry the residue at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of naproxen *(RS 244)*.

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1. The solutions should be protected from light.

Prepare a phosphate buffer pH 7.4 by dissolving 2.62 g of *sodium dihydrogen orthophosphate monohydrate* and 11.5 g of *anhydrous disodium hydrogen orthophosphate* in sufficient *water* to produce 1000 mL and adjusting the pH to 7.4, with either 0.1M *sodium hydroxide* or 0.1M *hydrochloric acid*, if necessary.

First stage

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

(1) After 2 hours, withdraw a 10-mL sample of the medium, filter through a 5-µm filter and measure the *absorbance* of the filtrate, Appendix II B, diluted with the dissolution medium, if necessary, at 332 nm using 0.1M *hydrochloric acid* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *naproxen BPCRS* in the phosphate buffer pH 7.4.

DETERMINATION OF CONTENT

Calculate the total content of naproxen, $C_{14}H_{14}O_3$, in the medium using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

LIMITS

The amount of naproxen released is not more than 5% of the stated amount.

Final stage

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Replace the 0.1M *hydrochloric acid* in the vessel with 900 mL of the phosphate buffer pH 7.4, previously held at 36.5° to 37.5°.

PROCEDURE

(1) After 45 minutes, withdraw a 10-mL sample of the medium and filter. Immediately measure the *absorbance* of the filtrate, Appendix II B, diluted with the phosphate buffer pH 7.4, if necessary, at 332 nm using the phosphate buffer pH 7.4 in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *naproxen BPCRS* in the phosphate buffer pH 7.4.

DETERMINATION OF CONTENT

Calculate the total content of naproxen, $C_{14}H_{14}O_3$, in the medium using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

LIMITS

The amount of naproxen released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be freshly prepared and protected from light.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 30 mg of Naproxen with 40 mL of the mobile phase, dilute with sufficient mobile phase to produce 50 mL and filter.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Further dilute 1 volume of this solution to 10 volumes with the mobile phase.

(3) 0.03% w/v of *naproxen impurity standard BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Nucleosil 120-3 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 50°.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use an autosampler temperature of 8°.

(f) Use a detection wavelength of 230 nm.

(g) Inject 20 µL of each solution.

(h) Allow the chromatography to proceed for 10 times the retention time of naproxen.

MOBILE PHASE

42 volumes of *acetonitrile* and 58 volumes of 0.01M *potassium dihydrogen orthophosphate* previously adjusted to pH 2.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to naproxen (retention time about 2 minutes) are: impurity O, about 0.8; impurity K, about 0.9; impurity L, about 1.5 and impurity N, about 5.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity K and naproxen is at least 2.2;

in the chromatogram obtained with solution (2), the *signal-to-noise* ratio of the peak due to naproxen is at least 50.

LIMITS

In the chromatogram obtained with solution (1), identify any peaks corresponding to impurities L, N and O using the chromatogram obtained with solution (3), and multiply the areas of these peaks by the following correction factors: L, 3.5 and O, 1.8.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.16%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. The solutions should be protected from light.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 0.1 g of Naproxen with 10 mL of *water*. Add 80 mL of *acetonitrile* and further mix. Dilute to produce 100 mL with *acetonitrile*. Dilute 1 volume of the filtrate to 100 volumes with the mobile phase and filter.

(2) 0.001% w/v of *naproxen BPCRS* in the mobile phase.

(3) 0.03% w/v of *naproxen impurity standard BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity K and naproxen is at least 2.2.

DETERMINATION OF CONTENT

Calculate the content of naproxen, $C_{14}H_{14}O_3$, in the tablets from the chromatograms obtained and using the declared content of $C_{14}H_{14}O_3$ in *naproxen BPCRS*.

STORAGE

Naproxen Gastro-resistant Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Naproxen.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Omeprazole Gastro-resistant Tablets

General Notices

Gastro-resistant Omeprazole Tablets

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Omeprazole Gastro-resistant Tablets contain Omeprazole. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of omeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of powdered tablets containing 20 mg of Omeprazole with 50 mL of 0.1M *sodium hydroxide*, dilute to 100 mL, filter and further dilute 10 mL to 100 mL. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits two maxima at 276 nm and 305 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1.

Mix 11 volumes of 0.25M *trisodium orthophosphate* and 22 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 100 volumes with *water* and adjust the pH, if necessary, to 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution A).

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution B).

Mix 5.2 volumes of 1M *anhydrous sodium dihydrogen orthophosphate* and 63.2 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 1000 volumes with *water* and adjust the pH, if necessary, to 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution C).

www.webofpharma.com

https://thuocngocanh.com/

First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use as the medium 700 mL of *0.05M phosphate buffer solution pH 4.5*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw 5 mL of the medium, filter the aliquot, dilute to 25 mL with solution A and retain the samples for analysis. Proceed immediately to the final stage.

(2) Dissolve a sufficient quantity of *omeprazole BPCRS* in solution A and dilute with *water*; the concentration of the final solution should be the same as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable). Use a suitable guard column.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.25 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 302 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 8 times the retention time of omeprazole.

MOBILE PHASE

25 volumes of solution C, 35 volumes of *water* and 40 volumes of *acetonitrile*. Adjust the pH, if necessary, to 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is not more than 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of omeprazole released is not more than 10% of the stated amount.

Final stage (pH 6.8)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 5 minutes of medium withdrawal at the first stage, add 200 mL of solution B at 37° to the vessel.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute 1 volume to 5 volumes with solution A and retain the samples for analysis.

(2) Dissolve a sufficient quantity of *omeprazole BPCRS* in solution A and dilute with *water*; the concentration of the final solution should be the same as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of omeprazole released after the final stage is not less than 65% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase. The solutions should be prepared immediately before use.

(1) Disperse a quantity of the powdered tablets containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix and filter.

(2) Dilute 5 volumes of solution (1) to 100 volumes. Dilute 1 volume of this solution to 10 volumes.

(3) 0.01% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil RP8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 40 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of omeprazole.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of a 0.14% w/v solution of *disodium hydrogen orthophosphate*, previously adjusted to pH 7.6 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with respect to omeprazole (retention time about 9 minutes) are: impurity D, about 0.8; impurity C, about 3.4.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is greater than 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%)

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Disperse a quantity of the powdered tablets containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix, filter and further dilute 1 volume to 10 volumes.
(2) 0.0012% w/v of *omeprazole BPCRS*.
(3) 0.01% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but with a detection wavelength of 305 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is greater than 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_3O_3S$ in the tablets from the chromatograms obtained and using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

IMPURITIES

The impurities limited by this monograph include those listed under Omeprazole.

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Omeprazole Gastro-resistant Capsules

General Notices

Gastro-resistant Omeprazole Capsules

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Omeprazole Gastro-resistant Capsules contain Omeprazole. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of omeprazole, $C_{17}H_{19}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the finely powdered contents of the capsules containing 20 mg of Omeprazole with 50 mL of 0.1M *sodium hydroxide*, dilute to 100 mL, filter and further dilute 10 mL to 100 mL. The *light absorption*, Appendix II B, in the range 230 to 350 nm exhibits two maxima, at 276 nm and 305 nm.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1.

Mix 11 volumes of 0.25M *trisodium orthophosphate* and 22 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 100 volumes with *water* and adjust the pH, if necessary, to 11.0 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution A).

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution B).

Mix 5.2 volumes of 1M *anhydrous sodium dihydrogen orthophosphate* and 63.2 volumes of 0.5M *anhydrous disodium hydrogen orthophosphate*, dilute to 1000 volumes with *water* and adjust the pH, if necessary, to 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate (solution C).

www.webofpharma.com

https://thuocngocanh.com/

First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use as the medium 700 mL of *0.05M phosphate buffer solution pH 4.5*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw 5 mL of the medium, filter the aliquot, dilute to 25 mL with solution A and retain the samples for analysis. Proceed immediately to the final stage.

(2) Dissolve a sufficient quantity of *omeprazole BPCRS* in solution A and dilute with *water*; the concentration of the final solution should be the same as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable). Use a suitable guard column.

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.25 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 302 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 8 times the retention time of omeprazole.

MOBILE PHASE

25 volumes of solution C, 35 volumes of *water* and 40 volumes of *acetonitrile*. Adjust the pH, if necessary, to 7.6 with *orthophosphoric acid* or 10M *sodium hydroxide*, as appropriate.

SYSTEM SUITABILITY

The *symmetry factor* of the peak due to omeprazole is not more than 2.0.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of omeprazole released is not more than 10% of the stated amount.

Final stage (pH 6.8)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 5 minutes of medium withdrawal at the first stage, add 200 mL of solution B at 37° to the vessel.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Dilute 1 volume to 5 volumes with solution A and retain the samples for analysis.

(2) Dissolve a sufficient quantity of *omeprazole BPCRS* in solution A and dilute with *water*; the concentration of the final solution should be the same as that expected for solution (1).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of $C_{17}H_{19}N_3O_3S$ in the medium using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

LIMITS

The amount of omeprazole released after the final stage is not less than 65% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase. The solutions should be prepared immediately before use.

(1) Disperse a quantity of finely powdered capsule contents containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix and filter.

(2) Dilute 5 volumes of solution (1) to 100 volumes. Dilute 1 volume of this solution to 10 volumes.

(3) 0.01% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Nucleosil RP8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 40 µL of each solution.

(g) Allow the chromatography to proceed for 5 times the retention time of omeprazole.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of a 0.14% w/v solution of *disodium hydrogen orthophosphate* previously adjusted to pH 7.6 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with respect to omeprazole (retention time about 9 minutes) are: impurity D, about 0.8; impurity C, about 3.4.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is at least 3.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity C is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%)

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Weigh and powder the contents of 20 capsules. Shake a quantity of the mixed capsule contents containing 24 mg of Omeprazole in 150 mL of mobile phase, mix with the aid of ultrasound for 30 minutes, dilute with sufficient mobile phase to produce 200 mL, mix and filter and further dilute 1 volume to 10 volumes.
(2) 0.0012% w/v of *omeprazole BPCRS*.
(3) 0.01% w/v each of *omeprazole BPCRS* and *omeprazole impurity D EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but with a detection wavelength of 305 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and omeprazole is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{19}N_3O_3S$ in the capsules using the declared content of $C_{17}H_{19}N_3O_3S$ in *omeprazole BPCRS*.

IMPURITIES

The impurities limited by this monograph include those listed under Omeprazole.

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Pancreatin Gastro-resistant Tablets

General Notices

Pancreatin Tablets

Gastro-resistant Pancreatin Tablets

Action and use

Enzyme; treatment of pancreatic exocrine deficiency.

DEFINITION

Pancreatin Gastro-resistant Tablets contain Pancreatin. They are made gastro-resistant by enteric-coating or by other means.

PRODUCTION

A validated dissolution test capable of characterising the *in vitro* release of pancreatin, relevant to the dosing schedule recommended by the manufacturer, should be applied to demonstrate batch to batch consistency in dissolution characteristics.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pancreatin

Not less than 90.0% of the stated minimum numbers of Units of free protease activity, of lipase activity and of amylase activity.

IDENTIFICATION

A. The tablets demonstrate free protease activity in the Assay for Free protease activity.

B. Triturate a quantity of powdered tablets containing 2.5 g of Pancreatin with 100 mL of *water* and filter. Adjust 10 mL of the filtrate to pH 8.0 by the addition of 1M *sodium hydroxide* using *cresol red solution* as indicator. Divide the resulting solution into two equal portions. Boil one portion [solution (1)] and leave the other untreated [solution (2)]. Dissolve 0.1 g of *soluble starch* in 100 mL of boiling *water*, boil for 2 minutes, cool and dilute to 150 mL with *water*. Add solution (1) to half the starch mucilage and solution (2) to the remainder and maintain the mixtures at 38° to 40° for 5 minutes. To 1 mL of each mixture add 10 mL of *iodinated potassium iodide solution*. The liquid containing solution (2) retains the colour of the solution of iodine and the liquid containing solution (1) acquires an intense blue colour.

ASSAY

Weigh and powder 20 tablets. Carry out the *Assay of pancreatin,* Appendix XIV I, for Free protease activity, Lipase activity and Amylase activity.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Pancreatin Gastro-resistant Tablets should be stored at a temperature not exceeding 15°, unless otherwise justified and authorised.

LABELLING

The label states the minimum number of Units of free protease activity, of lipase activity and of amylase activity in each tablet.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Pantoprazole Gastro-resistant Tablets

General Notices

Gastro-resistant Pantoprazole Tablets

Action and use

Proton pump inhibitor; treatment of peptic ulcer disease.

DEFINITION

Pantoprazole Gastro-resistant Tablets contain Pantoprazole Sodium Sesquihydrate. They are covered with a gastro-resistant coating or prepared from granules or particles covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pantoprazole, $C_{16}H_{15}F_2N_3O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing the equivalent of 50 mg of pantoprazole with 10 mL of *acetone*, filter (Whatman GF/C is suitable) and evaporate to dryness. Dry the residue at 60° for 30 minutes. The *infrared absorption spectrum* Appendix II A, is concordant with the reference spectrum of pantoprazole sodium *(RS 488)*.

TESTS

Dissolution

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1.

First stage (pH 4.5)

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use as the medium 700 mL of *0.05M phosphate buffer solution pH 4.5*.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuvienthuocngocanh.com/

(1) After 45 minutes, withdraw a sample of the medium, and filter the aliquot (0.45-µm PVDF is suitable). Dilute 1 volume of the filtrate to 5 volumes with *water*, and further dilute, if necessary, with sufficient *water* to produce a solution expected to contain about 0.00057% w/v of pantoprazole. Proceed immediately to the final stage.

(2) 0.0006% w/v of *pantoprazole sodium BPCRS* in *water*.

(3) 0.0018% w/v of *pantoprazole sodium BPCRS* and 0.0002% w/v of *pantoprazole impurity A BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution using the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 290 nm.

(g) Inject 50 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of 0.01M *dipotassium hydrogen phosphate trihydrate*, previously adjusted to pH 7.0 with a 20% v/v solution of *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pantoprazole is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of $C_{16}H_{15}F_2N_3O_4S$ in the medium using the declared content of $C_{16}H_{15}F_2N_3O_4S$ in *pantoprazole sodium BPCRS*.

LIMITS

The amount of pantoprazole released is not more than 10% of the stated amount.

Final stage (about pH 6.8)

Mix 1 volume of 10M *sodium hydroxide* with 99 volumes of *0.05M phosphate buffer solution pH 4.5* (solution A).

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Within 5 minutes of completion of the first stage, add to the vessel 200 mL of solution A, previously held and maintained at 37°.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) After 45 minutes, withdraw a sample of the medium, and filter the aliquot (0.45-µm PVDF is suitable). Dilute 1 volume of the filtrate to 5 volumes with *water*, and further dilute, if necessary, with sufficient *water* to produce a solution expected to contain about 0.00044% w/v of pantoprazole.

(2) 0.00047% w/v of *pantoprazole sodium BPCRS* in *water*.

(3) 0.0018% w/v of *pantoprazole sodium BPCRS* and 0.0002% w/v of *pantoprazole impurity A BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pantoprazole is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of $C_{16}H_{15}F_2N_3O_4S$ in the medium using the declared content of $C_{16}H_{15}F_2N_3O_4S$ in *pantoprazole sodium BPCRS*.

LIMITS

The amount of pantoprazole released is not less than 65% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 40 volumes of mobile phase B and 60 volumes of mobile phase A.

(1) Shake a quantity of whole tablets containing the equivalent of 0.16 g of pantoprazole in 50 mL, mix with the aid of ultrasound and dilute to produce 100 mL. Dilute 5 volumes to 20 volumes.

(2) Dilute 1 volume of solution (1) to 20 volumes. Dilute 1 volume of this solution to 10 volumes.

(3) 0.05% w/v of *pantoprazole for system suitability EPCRS*.

(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 290 nm.

(g) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.174% w/v solution of *disodium hydrogen orthophosphate*, previously adjusted to pH 7.0 with *orthophosphoric acid*.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase B 48 volumes of mobile phase A and 52 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	60	40	isocratic
3-43	60→40	40→60	linear gradient
43-48	40→60	60→40	linear gradient
48-55	60	40	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to pantoprazole (retention time about 16 minutes) are: impurity C, about 0.4; impurity A, about 0.8; impurity D + F, about 1.3; impurity E, about 2.0 and impurity B, about 2.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to pantoprazole and impurity D + F is greater than 3.0.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity C using the chromatogram obtained with solution (3) and multiply the area of this peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A and impurity D + F (combined peak area) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5% of each);

the area of any other *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Prepare a solution containing equal volumes of *acetonitrile* and 0.001M *sodium hydroxide* (solution B).

(1) Shake 10 tablets with 50 mL of solution B, mix with the aid of ultrasound and dilute to 100 mL with solution B. Centrifuge and dilute the supernatant liquid with solution B to give a solution containing the equivalent of 0.004% w/v of pantoprazole.
(2) 0.0045% w/v of *pantoprazole sodium BPCRS* in solution B.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.0045% w/v of *pantoprazole sodium BPCRS* and 0.0005% w/v of *pantoprazole impurity A BPCRS* in solution B.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used with an injection volume of 20 µL.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and pantoprazole is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{15}F_2N_3O_4S$ in the tablets from the chromatograms obtained and using the declared content of $C_{16}H_{15}F_2N_3O_4S$ in *pantoprazole sodium BPCRS*.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of pantoprazole.

IMPURITIES

The impurities limited by this monograph include those listed under Pantoprazole Sodium Sesquihydrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Prednisolone Gastro-resistant Tablets

General Notices

Gastro-resistant Prednisolone Tablets

Action and use

Glucocorticoid.

DEFINITION

Prednisolone Gastro-resistant Tablets contain Prednisolone. They are covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of prednisolone, $C_{21}H_{28}O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets with *dichloromethane*, filter and evaporate the filtrate to dryness. The residue complies with the test for *identification of steroids*, Appendix III A, using *impregnating solvent I* and *mobile phase A*.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak having the same retention time as the peak due to prednisolone in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

Use the apparatus described under Test A for the *disintegration test for tablets and capsules*, Appendix XII A1, introduce one tablet into each of six tubes and operate the apparatus without the discs for 60 minutes in 0.1M *hydrochloric acid*. Remove the tablets and use these tablets to carry out the dissolution test as described below.

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *mixed phosphate buffer pH 6.8*, at a temperature of 37°, as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of 20 mL of the medium and filter through a membrane filter having a nominal pore size not greater than 0.45 µm, discarding the first 10 mL of filtrate.

(2) Prepare a 0.05% w/v solution of *prednisolone BPCRS* in a mixture of 42 volumes of *water* and 58 volumes of *methanol* and dilute with the dissolution medium to contain 0.00025% w/v of prednisolone.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (10 µm) (Spherisorb ODS 1 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

42 volumes of *water* and 58 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *column efficiency*, determined using the peak due to prednisolone, is greater than 15,000 *theoretical plates* per metre.

DETERMINATION OF CONTENT

Calculate the total content of prednisolone, $C_{21}H_{28}O_5$, in the medium using the declared content of $C_{21}H_{28}O_5$ in *prednisolone BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 10 mg of Prednisolone with 25 mL of *methanol* for 10 minutes and mix with the aid of ultrasound for 2 minutes. Filter the extract (Whatman GF/F is suitable), wash the filter with two 10-mL quantities of *methanol*, combine the filtrate and washings and evaporate to dryness using a rotary evaporator and a warm water bath; dissolve the residue in 10 mL of *tetrahydrofuran* and dilute to 20 mL with *water*.

(2) 0.002% w/v each of *prednisolone BPCRS* and *hydrocortisone BPCRS* in the mobile phase.

(3) Dilute 1 volume of solution (1) to 100 volumes with a 50% v/v solution of *tetrahydrofuran*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Alltima C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 45°.

www.webofpharma.com

https://thuocngocanh.com/

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1) allow the chromatography to proceed for 4.5 times the retention time of the principal peak.

When the chromatograms are recorded in the prescribed conditions, the retention times are: prednisolone, about 14 minutes and hydrocortisone, about 15.5 minutes.

MOBILE PHASE

Mix 220 volumes of *tetrahydrofuran* with 700 volumes of *water*, allow to equilibrate and dilute to 1000 volumes with *water* and mix.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to prednisolone and hydrocortisone is at least 2.2. If necessary, adjust the concentration of *tetrahydrofuran* in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1%);

the sum of the areas of any such peaks is not greater than four times the area of the principal peak in the chromatogram obtained with solution (3) (4%).

Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%) and any peak with a retention time of 5 minutes or less.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 58 mL of *methanol* to a quantity of the powdered tablets containing 5 mg of Prednisolone, shake for 10 minutes, add sufficient *water* to produce 100 mL, mix and filter.

(2) Dissolve 5 mg of *prednisolone BPCRS* in 58 mL of *methanol* and dilute to 100 mL with *water*.

(3) Add 10 mL of a 0.075% w/v solution of *dexamethasone* in *methanol* and 48 mL of *methanol* to a quantity of the powdered tablets containing 5 mg of Prednisolone, shake for 10 minutes, add sufficient *water* to produce 100 mL, mix and filter.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The assay is not valid unless, in the chromatogram obtained with solution (3):

the *resolution factor* between the peaks due to prednisolone and dexamethasone is at least 2.5;

the *column efficiency*, determined using the peak due to prednisolone, is greater than 15,000 *theoretical plates* per metre.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of $C_{21}H_{28}O_5$ in the tablets using the declared content of $C_{21}H_{28}O_5$ in *prednisolone BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Sodium Valproate Gastro-resistant Tablets

General Notices

Gastro-resistant Sodium Valproate Tablets

Sodium Valproate Gastro-resistant Tablets from different manufacturers, whilst complying with the requirements of the monograph, may not be interchangeable.

Action and use

Antiepileptic.

DEFINITION

Sodium Valproate Gastro-resistant Tablets contain Sodium Valproate. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sodium valproate, $C_8H_{15}NaO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 10 mL of *water* and centrifuge. Acidify 5 mL of the supernatant liquid with 2M *sulfuric acid*, shake with 25 mL of *dichloromethane* and wash the dichloromethane layer with 5 mL of *water*. Dry by shaking with *anhydrous sodium sulfate*, filter and evaporate the dichloromethane to dryness. The *infrared absorption spectrum* of a thin film of the residue, Appendix II A, is concordant with the *reference spectrum* of valproic acid (*RS 431*).

B. Shake a quantity of the powdered tablets containing 0.25 g of Sodium Valproate with 3 mL of *water* and centrifuge. To 2 mL of the supernatant liquid add 0.5 mL of a 10% w/v solution of *cobalt(II) nitrate*. A purple precipitate is produced which is soluble in *dichloromethane*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

First stage

www.webofpharma.com

https://thuocngocanh.com/

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Use 900 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 2 hours, withdraw a 20-mL sample of the medium and filter.

(2) 0.001% w/v of *sodium valproate BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (µBondapak C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

45 volumes of a 0.32% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 3.0 with *orthophosphoric acid* and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of sodium valproate, $C_8H_{15}NaO_2$, in the medium using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

LIMITS

The amount of sodium valproate released is not more than 5% of the stated amount.

Final stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.

(b) Replace the *0.1M hydrochloric acid* in the vessel with 900 mL of *phosphate buffer pH 6.8*, previously held at 37°, as the medium.

PROCEDURE

(1) After 60 minutes, withdraw a 20-mL sample of the medium and filter. Use the filtrate diluted, if necessary, to give a solution expected to contain 0.002% w/v of Sodium Valproate.

(2) 0.02% w/v solution of *sodium valproate BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under the first stage may be used.

DETERMINATION OF CONTENT

Calculate the total content of sodium valproate, $C_8H_{15}NaO_2$, in the medium using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

The amount of sodium valproate released after the final stage is not less than 70% of the stated amount.

Related substances

Carry out the method for *gas chromatography*, Appendix III B, using the following solutions.

(1) 0.005% w/v of *octanoic acid* in *dichloromethane* (internal standard solution).

(2) Disperse a quantity of the powdered tablets containing 1 g of Sodium Valproate with 20 mL of 0.1M *sodium hydroxide*, and mix with the aid of ultrasound for 30 minutes. Centrifuge the solution and transfer 10 mL of the supernatant into a separating funnel. Mix the resulting solution with 1 mL of 2M *sulfuric acid* and add 10 mL of solution (1). Extract the mixture with three 20-mL quantities of *dichloromethane* and combine the organic layers. Dry by shaking with *anhydrous sodium sulfate*, and filter (a GF/A filter is suitable). Reduce the volume of the filtrate at a temperature not exceeding 30° and dilute to 10 mL with *dichloromethane*.

(3) Dilute 1 volume of solution (2) to 100 volumes with solution (1). Dilute 1 volume of the resulting solution to 10 volumes with solution 1.

(4) 5% w/v of *valproic acid for system suitability EPCRS* in *dichloromethane*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a fused silica capillary column (30 m × 0.53 mm) bonded with a 0.5-µm layer of *macrogol 20,000 2-nitroterephthalate* (DB-FFAP is suitable).

(b) Use *helium* as the carrier gas at 8 mL per minute.

(c) Use the temperature gradient conditions as described below.

(d) Use an injection temperature of 220°.

(e) Use a flame ionisation detector at 220°.

(f) Inject 1 µL of each solution.

(g) Use a split ratio of 1:10.

Time (Minutes)	Temperature (°C)	Comment
0-5	80	isothermal
5-15	80→150	linear gradient
15-28.3	150→190	linear gradient
28.3-30	190	isothermal
30-35	190→250	linear gradient
35-45	250	isothermal

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to valproic acid (retention time, about 15 minutes) are: impurity K, about 0.97; octanoic acid, about 1.12.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity K and valproic acid is at least 2.0.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

Using the chromatogram obtained with solution (3), calculate the ratio of the area of the peak due to valproic acid to the area of the peak due to the internal standard (*R*).

In the chromatogram obtained with solution (2):

the ratio of the area of the peak due to impurity K to the area of the peak due to the internal standard is not greater than 2*R* (0.2%);

the ratio of the area of any *secondary peak* to the area of the peak due to the internal standard is not greater than *R* (0.1%);

the ratio of the sum of the areas of any *secondary peaks* to the area of the peak due to the internal standard is not greater than 4*R* (0.4%).

Disregard any peak where the ratio of the area of any peak to the area of the peak due to the internal standard is not greater than half of *R* (0.05%) and any peak eluting after 30 minutes.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D using the following solutions.

Solution A: Dissolve 6.8 g of *potassium dihydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 6.8 with 0.2M *sodium hydroxide*.

(1) Weigh and powder 20 tablets. Shake with the aid of ultrasound a quantity of the powdered tablets containing 0.5 g of Sodium Valproate with 50 mL of *acetonitrile R1*. Add 100 mL of solution A and mix further with the aid of ultrasound. Dilute the solution to 200 mL and filter (a 0.2-µm nylon syringe filter is suitable). Dilute 1 volume of this solution to 5 volumes with solution A.
(2) Mix with the aid of ultrasound 50 mg of *sodium valproate BPCRS* with 5 mL of *acetonitrile R1*. Add 10 mL of solution A and mix further with the aid of ultrasound. Dilute the resulting solution to 100 mL with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 25°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *acetonitrile R1* and 50 volumes of a solution prepared by dissolving 1.56 g of *sodium dihydrogen orthophosphate* in 1000 mL of *water* and adjusting the pH to 2.3 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of $C_8H_{15}NaO_2$ in the tablets using the declared content of $C_8H_{15}NaO_2$ in *sodium valproate BPCRS*.

IMPURITIES

www.webofpharma.com

https://thuocngocanh.com/

The impurities limited by the requirements of this monograph include those listed under Sodium Valproate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Sulfasalazine Gastro-resistant Tablets

General Notices

Gastro-resistant Sulfasalazine Tablets

Action and use

Aminosalicylate; treatment of ulcerative colitis.

DEFINITION

Sulfasalazine Gastro-resistant Tablets contain Sulfasalazine. They are covered with a gastro-resistant coating.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of sulfasalazine, $C_{18}H_{14}N_4O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract for 30 minutes with the aid of ultrasound a quantity of the powdered tablets containing 0.2 g of Sulfasalazine with 100 mL of *methanol*, filter, evaporate the filtrate to dryness and dry at 35° at a pressure of 2 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of sulfasalazine *(RS 429)*.

B. In the test for Related substances, the principal peak in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (4).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of a phosphate buffer prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 1.66 g of *sodium hydroxide* in sufficient *water* to produce 1000 mL and adjusting the pH to 7.5 with 5M *sodium hydroxide*, if necessary, at a temperature of 37° as the medium.

PROCEDURE

www.webofpharma.com

https://thuocngocanh.com/

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.005% w/v of Sulfasalazine, at the maximum at 406 nm, Appendix II B using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.005% w/v solution of *sulfasalazine BPCRS* in dissolution medium, using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of sulfasalazine, $C_{18}H_{14}N_4O_5S$, in the medium from the absorbances obtained and using the declared content of $C_{18}H_{14}N_4O_5S$ in *sulfasalazine BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Sulfasalazine with 100 mL of 0.1M *ammonia* for 30 minutes, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes with 0.1M *ammonia*.

(3) 0.001% w/v of *sulfasalazine derivative for resolution EPCRS* in solution (2).

(4) 0.001% w/v of *sulfasalazine BPCRS* in 0.1M *ammonia*.

(5) Dilute 1 volume of solution (2) to 20 volumes with 0.1M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use ambient column temperature.

(e) Use a detection wavelength of 320 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.013% w/v of *sodium dihydrogen orthophosphate* and 0.25% w/v of *sodium acetate* adjusted to pH 4.8 with *glacial acetic acid*.

Mobile phase B 1 volume of mobile phase A and 4 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	60→45	40→55	linear gradient
15-25	45	55	isocratic
25-60	45→0	55→100	linear gradient

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
60-65	0	100	isocratic
65-67	0→60	100→40	linear gradient
67-77	60	40	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retentions relative to sulfasalazine (retention time about 24 minutes) are: salicylic acid (impurity H), about 0.16; impurity I, about 0.28; impurity C, about 0.80; impurity F, about 0.85; impurity G, about 1.39; impurity E, about 1.63; impurity B, about 1.85; impurity D, about 1.90 and impurity A, about 2.00.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks corresponding to sulfasalazine and sulfasalazine derivative for resolution is at least 3.

LIMITS

In the chromatogram obtained with solution (1);

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4%).

Disregard any peak with a retention time less than 6 minutes (corresponding to salicylic acid and sulfapyridine) and any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

Salicylic acid and sulfapyridine

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.1 g of Sulfasalazine with 100 mL of 0.1M *ammonia* for 30 minutes, centrifuge and use the supernatant liquid.
(2) 0.001% w/v of *salicylic acid* and 0.001% w/v of *sulfapyridine EPCRS* in 0.1M *ammonia*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use ambient column temperature.
(e) Use a detection wavelength of 300 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 10 minutes.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

A mixture of 30 volumes of mobile phase B and 70 volumes of mobile phase A described in the test for Related substances.

When the chromatograms are recorded under the prescribed conditions the retention time of salicylic acid is about 6 minutes and that of sulfapyridine is about 7 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peaks corresponding to salicylic acid and sulfapyridine is at least 2.

LIMITS

In the chromatogram obtained with solution (1), the areas of any peaks corresponding to salicylic acid and sulfapyridine are not greater than half the areas of the corresponding peaks in the chromatogram obtained with solution (2) (0.5% of each).

ASSAY

Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.15 g of Sulfasalazine with about 50 mL of 0.1M *sodium hydroxide*, add sufficient of the same solvent to produce 100 mL, filter and discard the first 20 mL of filtrate. Dilute 5 mL of the filtrate with 750 mL of *water*, add 20 mL of 0.1M *acetic acid*, mix and add sufficient *water* to produce 1000 mL. Measure the *absorbance* of this solution at the maximum at 359 nm, Appendix II B. Calculate the content of $C_{18}H_{14}N_4O_5S$ in the tablets from the *absorbance* of a standard solution prepared in the same manner using 0.15 g of *sulfasalazine BPCRS* and using the declared content of $C_{18}H_{14}N_4O_5S$ in *sulfasalazine BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Sulfasalazine.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Aspirin Gastro-resistant Tablets

General Notices

Gastro-resistant Aspirin Tablets

Action and use

Salicylate; non-selective cyclo-oxygenase inhibitor; antipyretic; analgesic; anti-inflammatory.

DEFINITION

Aspirin Gastro-resistant Tablets contain Aspirin. They are made gastro-resistant by enteric-coating or by other means.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of aspirin, $C_9H_8O_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Aspirin with 20 mL of *absolute ethanol*, filter (Whatman GF/C is suitable), evaporate the filtrate and dry the residue at 60° for 1 hour. The *infrared absorption spectrum* of the residue, is concordant with the *reference spectrum* of aspirin *(RS 483)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

First stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 1000 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 2 hours, withdraw a sample of the medium, filter and measure the *absorbance* of the filtrate, Appendix II B, at 276 nm using 0.1M *hydrochloric acid* in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *aspirin BPCRS* in 0.1M *hydrochloric acid*.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the total content of aspirin, $C_9H_8O_4$, in the medium using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*. The amount of aspirin released is not more than 5% of the stated amount.

Final stage

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Replace the 0.1M *hydrochloric acid* in the vessel with 900 mL of *mixed phosphate buffer pH 6.8*, previously held at 36.5° to 37.5°.

PROCEDURE

(1) After 45 minutes, withdraw a sample of the medium and filter. Immediately measure the *absorbance* of the filtrate, Appendix II B, diluted with the dissolution medium, if necessary, at 265 nm using dissolution medium in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *aspirin BPCRS* in the dissolution medium.

DETERMINATION OF CONTENT

Calculate the total content of aspirin, $C_9H_8O_4$, in the medium using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 0.10 g of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.
(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(3) 0.003% w/v of *salicylic acid* (impurity C) in the mobile phase.
(4) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 237 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 1.2 times the retention time of impurity F.

MOBILE PHASE

2 volumes of *orthophosphoric acid*, 400 volumes of *acetonitrile* and 600 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to aspirin (retention time about 5 minutes) are: impurity A, about 0.6; impurity B, about 0.7, impurity C, about 1.4 and impurity F, about 8.0.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (4) the *resolution* between the peaks due to aspirin and impurity C is at least 6.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%);

the area of any other *secondary peak* is not greater than half of the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *Liquid Chromatography*, Appendix III D, using the following solutions.

(1) Mix with the aid of ultrasound for 15 minutes a quantity of the powdered tablets containing 60 mg of Aspirin with 40 mL of *acetonitrile*, allow to cool, dilute to 100 mL with *water* and filter through a 0.45-µm PTFE filter.
(2) 0.06% w/v of *aspirin BPCRS* in the mobile phase.
(3) 0.1% w/v of *aspirin impurity standard BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) the *resolution* between the peaks due to aspirin and impurity C is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_9H_8O_4$ in the tablets from the chromatograms obtained using the declared content of $C_9H_8O_4$ in *aspirin BPCRS*.

STORAGE

Aspirin Gastro-resistant Tablets should be protected from moisture.

LABELLING

The label states that the tablets contain Aspirin, unless this word appears in the name of the tablets (this requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed).

www.webofpharma.com

https://thuocngocanh.com/

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aspirin.

© Crown Copyright 2022

www.webofpharma.com

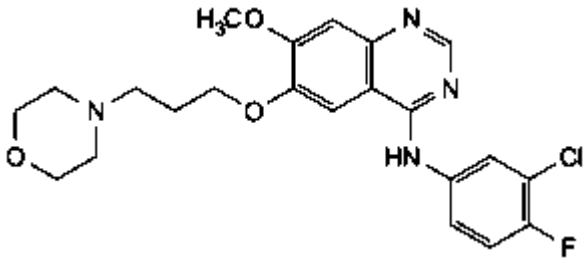
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gefitinib

General Notices

(Ph. Eur. monograph 2866)



$C_{22}H_{24}ClFN_4O_3$ 446.9 *184475-35-2*

Action and use

Cytotoxic.

Ph Eur

DEFINITION

N-(3-Chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *gefitinib CRS*.

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, 0.2 per cent *V/V* solution of trifluoroacetic acid R (40:60 *V/V*).

Test solution Dissolve 35.0 mg of the substance to be examined in 85 mL of the solvent mixture, with the aid of ultrasound, and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 35.0 mg of gefitinib CRS in 85 mL of the solvent mixture, with the aid of ultrasound, and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of gefitinib for system suitability CRS (containing impurity B) in 1.0 mL of the solvent mixture with the aid of ultrasound.

Column:

— *size*: *l* = 0.10 m, Ø = 3 mm;

— *stationary phase*: base-deactivated end-capped octadecylsilyl silica gel for chromatography R (3 µm);

— *temperature*: 60 °C.

Mobile phase acetonitrile R, 9.68 g/L solution of ammonium acetate R (38:62 *V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 247 nm.

Injection 5 µL of the test solution and reference solutions (b) and (c).

Run time 5 times the retention time of gefitinib.

Identification of impurities Use the chromatogram supplied with gefitinib for system suitability CRS and the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

Relative retention With reference to gefitinib (retention time = about 5.5 min): impurity B = about 1.3.

System suitability Reference solution (c):

— resolution: minimum 3.0 between the peaks due to gefitinib and impurity B.

Calculation of percentage contents:

www.webofpharma.com

https://thuocngocanh.com/

— for each impurity, use the concentration of gefitinib in reference solution (b).

Limits:

— *impurity B*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

Maximum 0.5 per cent, determined on 0.100 g by direct sample introduction.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

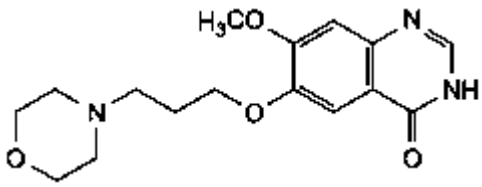
Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{22}H_{24}ClFN_4O_3$ taking into account the assigned content of *gefitinib CRS*.

IMPURITIES

Specified impurities *B*.

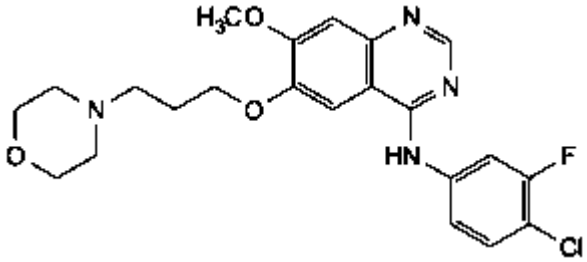
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A*.



A. 7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4(3*H*)-one,

www.webofpharma.com

https://thuocngocanh.com/



B. *N*-(4-chloro-3-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gelatin[1]

General Notices

(Ph. Eur. monograph 0330)

Action and use

Excipient.

Ph Eur

DEFINITION

Purified protein obtained from collagen of animals by partial alkaline and/or acid hydrolysis and/or enzymatic hydrolysis, or by thermal hydrolysis.

The hydrolysis leads to gelling or non-gelling product grades. This monograph covers both the gelling grade and the non-gelling grade (also called hydrolysed gelatin).

♦ CHARACTERS

Appearance

— *gelling grade*: faintly yellow or light yellowish-brown solid, usually occurring as translucent sheets, shreds, granules or powder;

— *non-gelling grade*: faintly yellow or white granules or powder.

Solubility

— *gelling grade*: practically insoluble in common organic solvents; gelling grades swell in cold water and give on heating a colloidal solution which on cooling forms a more or less firm gel;

— *non-gelling grade*: soluble in cold or warm water, practically insoluble in common organic solvents.

Different gelatins form aqueous solutions that vary in clarity and colour. For a particular application, a suitable specification for clarity and colour may be required.♦

IDENTIFICATION

Gelling grade: A, B.

Non-gelling grade: A, B, C.

www.webofpharma.com

https://thuocngocanh.com/

A. To 2 mL of solution S (see Tests) add 0.05 mL of *copper sulfate solution R*. Mix and add 0.5 mL of *dilute sodium hydroxide solution R*. A violet colour is produced.

B. In a test-tube about 15 mm in internal diameter, place 0.5 g of the substance to be examined and add 10 mL of *water R*. Allow to stand for 10 min, heat at 60 °C for 15 min and keep the tube upright at 2-8 °C for 6 h. Invert the tube; the contents flow out immediately for non-gelling grades and do not flow out immediately for gelling grades.

C. To 0.5 g in a 250 mL bottle, add 10 mL of *water R* and 5 mL of *sulfuric acid R*. Place the bottle, partly but not completely closed (for example, using a watch glass), in an oven at 105 °C for 4 h. Allow to cool and add 200 mL of *water R*. Adjust to pH 6.0-8.0 using a 200 g/L solution of *sodium hydroxide R*. Place 2 mL of the solution in a test-tube and add 2 mL of a solution prepared immediately before use containing 14 g/L of *chloramine R* in *phosphate buffer solution pH 6.8 R*. Mix and allow to stand for 20 min. Add 2 mL of *dimethylaminobenzaldehyde solution R9*. Mix and place in a water-bath at 60 °C for 15 min. A red to violet colour develops.

TESTS

Solution S

Dissolve 1.00 g in *carbon dioxide-free water R* at about 55 °C, dilute to 100 mL with the same solvent and keep the solution at this temperature to carry out the tests.

pH (*2.2.3*)

3.8 to 7.6 for solution S, measured at 55 °C.

Conductivity (*2.2.38*)

Maximum 1 $mS\text{-}cm^{-1}$, determined on a 10.0 g/L solution at 30 ± 1.0 °C (without the use of a temperature compensation device).

Sulfur dioxide (*2.5.29*)

Maximum 50 ppm.

Peroxides

Maximum 10 ppm, determined using *peroxide test strips R*.

Peroxidase transfers oxygen from peroxides to an organic redox indicator which is converted to a blue oxidation product. The intensity of the colour obtained is proportional to the quantity of peroxide and can be compared with a colour scale provided with the test strips, to determine the peroxide concentration.

Suitability test Dip a test strip for 1 s into *hydrogen peroxide standard solution (2 ppm H_2O_2) R*, such that the reaction zone is properly wetted. Remove the test strip, shake off excess liquid and after 15 s compare the reaction zone with the colour scale provided. The test strips are suitable if the colour matches that of the 2 ppm concentration.

Test Weigh 20.0 ± 0.1 g of the substance to be examined in a beaker and add 80.0 ± 0.2 mL of *water R*. Stir to moisten all the gelatin and allow the sample to stand at room temperature for 1-3 h. Cover the beaker with a watch-glass. If dissolution is not complete, place the beaker for 20 ± 5 min in a water-bath at 65 ± 2 °C to dissolve the sample. Stir the contents of the beaker with a glass rod to achieve a

www.webofpharma.com

https://thuocngocanh.com/

homogeneous solution. Dip a test strip for 1 s into the test solution, such that the reaction zone is properly wetted. Remove the test strip, shake off excess liquid and after 15 s compare the reaction zone with the colour scale provided. Multiply the concentration read from the colour scale by a factor of 5 to calculate the concentration in parts per million of peroxide in the substance to be examined.

Gel strength (Bloom value)

80 per cent to 120 per cent of the nominal value stated on the label for the gelling grade.

The gel strength is expressed as the mass in grams necessary to produce the force which, applied to a plunger 12.7 mm in diameter, makes a depression 4 mm deep in a gel having a concentration of 6.67 per cent *m/m* and matured at 10 °C.

Apparatus Texture analyser or gelometer with:

— a cylindrical piston 12.7 ± 0.1 mm in diameter with a plane pressure surface with a sharp bottom edge;

— a bottle 59 ± 1 mm in internal diameter and 85 mm high.

Adjust the apparatus according to the manufacturer's manual. Settings are: distance 4 mm, test speed 0.5 mm/s.

Method Place 7.5 g of the substance to be examined in a bottle. Add 105 mL of *water R*, close the bottle and allow to stand for 1-4 h. Heat in a water-bath at 65 ± 2 °C for 15 min. While heating, stir gently with a glass rod. Ensure that the solution is uniform and that any condensed water on the inner walls of the bottle is incorporated. Allow to cool at room temperature for 15 min and transfer the bottle to a thermostatically controlled bath at 10.0 ± 0.1 °C, fitted with a device to ensure that the platform on which the bottle stands is perfectly horizontal. Close the bottle and allow to stand for 17 ± 1 h. Remove the bottle from the bath and quickly wipe the water from the exterior of the bottle. Centre the bottle on the platform of the apparatus so that the plunger contacts the sample as near to its midpoint as possible and start the measurement.

Iron

Maximum 30 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution To 5.00 g of the substance to be examined, in a conical flask, add 10 mL of *hydrochloric acid R*. Close the flask and place in a water-bath at 75-80 °C for 2 h (if necessary for proper solubilisation, the gelatin may be allowed to swell after addition of the acid and before heating, the heating time may be prolonged, and a higher temperature may be used). Allow to cool and adjust the contents of the flask to 100.0 g with *water R*.

Reference solutions Prepare the reference solutions using *iron standard solution (8 ppm Fe) R*, diluting with *water R*.

Wavelength 248.3 nm.

Chromium

Maximum 10 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Test solution described in the test for iron.

Reference solutions Prepare the reference solutions using *chromium standard solution (100 ppm Cr) R*, diluting with *water R*.

Wavelength 357.9 nm.

Zinc

Maximum 30 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution Test solution described in the test for iron.

Reference solutions Prepare the reference solutions using *zinc standard solution (10 ppm Zn) R*, diluting with *water R*.

Wavelength 213.9 nm.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 5.000 g by drying in an oven at 105 °C for 16 h.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

STORAGE

Protected from heat and moisture.

LABELLING

The label states the gel strength (Bloom value) or that it is a non-gelling grade (also called hydrolysed gelatin).

◊ FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the

www.webofpharma.com

https://thuocngocanh.com/

purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for gelling grade gelatin used as viscosity-increasing agent, binder or used for microencapsulation.

Gel strength (Bloom value)

(see Tests).◊

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

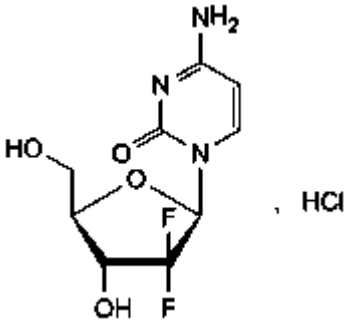
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gemcitabine Hydrochloride

General Notices

(Ph. Eur. monograph 2306)



$C_9H_{12}ClF_2N_3O_4$ 299.7 *122111-03-9*

Action and use

Pyrimidine analogue; cytotoxic.

Ph Eur

DEFINITION

4-Amino-1-(2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl)pyrimidin-2(1*H*)-one hydrochloride.

Content

98.0 per cent to 102.0 per cent.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Soluble in water, slightly soluble in methanol, practically insoluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *gemcitabine hydrochloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 100.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

pH (*2.2.3*)

2.0 to 3.0 for solution S.

Specific optical rotation (*2.2.7*)

+ 43.0 to + 50.0, determined on solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in *water R* and dilute to 200.0 mL with the same solvent.

Reference solution (a) Dissolve 10.0 mg of the substance to be examined and 10.0 mg of *gemcitabine impurity A CRS* in *water R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 20.0 mg of *gemcitabine hydrochloride CRS* in *water R* and dilute to 200.0 mL with the same solvent.

Reference solution (c) In order to prepare impurity B *in situ*, place 10 mg of the substance to be examined in a small vial, add 4 mL of a 168 g/L solution of *potassium hydroxide R* in *methanol R*, sonicate for 5 min then seal with a cap; the mixture may be cloudy; heat at 55 °C for a minimum of 6 h. Allow to cool, then transfer the entire contents of the vial to a 100 mL volumetric flask by successively washing with a 1 per cent *V/V* solution of *phosphoric acid R*. Dilute to 100 mL with a 1 per cent *V/V* solution of *phosphoric acid R* and mix.

Reference solution (d) Dissolve 10.0 mg of *gemcitabine impurity C CRS* in *water R* and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm).

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase:

— *mobile phase A*: 13.8 g/L solution of *sodium dihydrogen phosphate monohydrate R* adjusted to pH 2.5 ± 0.1 with *phosphoric acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	97	3
8 - 13	97 → 50	3 → 50
13 - 20	50	50

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 275 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to gemcitabine (retention time = about 7 min): impurity A = about 0.4; impurity B = about 0.7; impurity C = about 1.7.

System suitability Reference solution (c):

— *resolution*: minimum 8.0 between the peaks due to impurity B and gemcitabine.

Calculation of percentage contents:

— for impurity C, use the concentration of impurity C in reference solution (d);

— for impurity A, use the concentration of impurity A in reference solution (a);

— for impurities other than A and C, use the concentration of gemcitabine hydrochloride in reference solution (a).

Limits:

— *impurity C*: maximum 0.2 per cent;

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *reporting threshold*: 0.05 per cent.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase *methanol R*, mobile phase A (3:97 *V/V*).

Injection Test solution (b) and reference solution (b).

Relative retention With reference to gemcitabine (retention time = about 8 min): impurity B = about 0.5.

Calculate the percentage content of $C_9H_{12}ClF_2N_3O_4$ taking into account the assigned content of *gemcitabine hydrochloride CRS*.

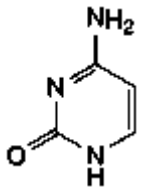
STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

IMPURITIES

Specified impurities *A, C.*

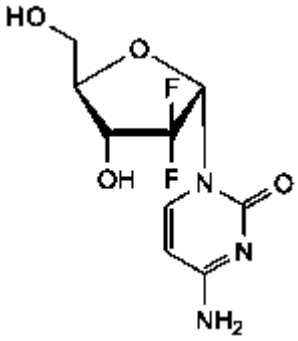
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B.*



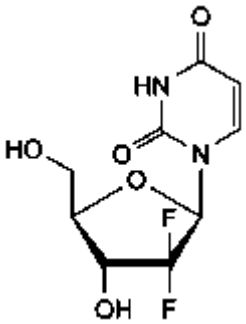
A. 4-aminopyrimidin-2(1*H*)-one (cytosine),

www.webofpharma.com

https://thuocngocanh.com/



B. 4-amino-1-(2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl)pyrimidin-2(1*H*)-one (gemcitabine α-anomer),



C. 1-(2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl)pyrimidin-2,4(1*H*,3*H*)-dione (2′-deoxy-2′,2′-difluorouridine).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

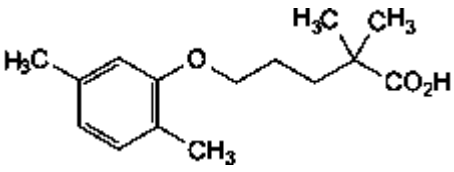
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gemfibrozil

General Notices

(Ph. Eur. monograph 1694)



$C_{15}H_{22}O_3$ 250.3 *25812-30-0*

Action and use

Fibrate; lipid-regulating drug.

Preparations

Gemfibrozil Capsules

Gemfibrozil Tablets

Ph Eur

DEFINITION

5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoic acid.

Content

99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, waxy, crystalline powder.

Solubility

Practically insoluble in water, very soluble in methylene chloride, freely soluble in anhydrous ethanol and in methanol.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Melting point (2.2.14): 58 °C to 61 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *gemfibrozil CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 40.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

Reference solution (a) Dissolve the contents of a vial of *gemfibrozil for system suitability CRS* (containing impurities C, D and E) in 2.0 mL of *acetonitrile R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve 5 mg of *2,5-dimethylphenol R* (impurity A) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 0.49 g of *potassium acetate R* in 400 mL of *water for chromatography R*, adjust to pH 4.0 with *phosphoric acid R* and add 600 mL of *acetonitrile R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 20	100 → 0	0 → 100
20 - 25	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 276 nm.

Injection 20 µL.

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram supplied with *gemfibrozil for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C, D and E; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention With reference to gemfibrozil (retention time = about 7 min): impurity A = about 0.4; impurity C = about 1.3; impurity D = about 1.5; impurity E = about 1.7; impurity I = about 2.0; impurity H = about 2.9.

System suitability Reference solution (a):

— *resolution*: minimum 6.0 between the peaks due to gemfibrozil and impurity C, and minimum 2.0 between the peaks due to impurities D and E.

Limits:

— *correction factors*: for the calculation of content multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.5; impurity D = 1.8; impurity E = 0.2; impurity H = 0.6;

— *impurities E, I*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities A, D, H*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.5.12)

Maximum 0.25 per cent, determined on 2.000 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 2.0 g. Allow to stand for 1 h after the first moistening before heating.

ASSAY

Dissolve 0.200 g in 40 mL of *methanol R*. Add 10 mL of *water R* and 1 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (2.2.20) using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 25.03 mg of $C_{15}H_{22}O_3$.

STORAGE

Protected from light.

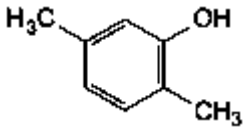
www.webofpharma.com

https://thuocngocanh.com/

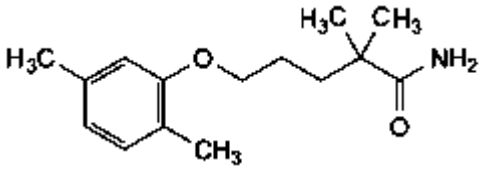
IMPURITIES

Specified impurities *A, D, E, H, I.*

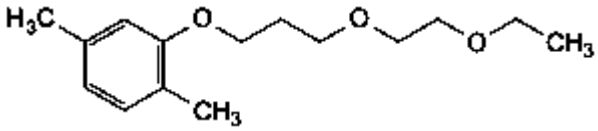
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, F, G.*



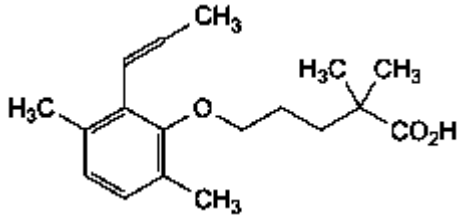
A. 2,5-dimethylphenol (*p*-xylenol),



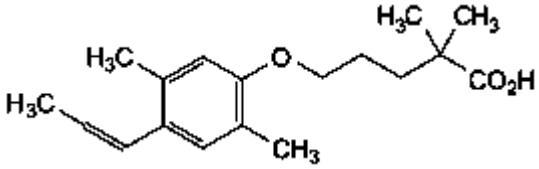
B. 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanamide,



C. 2-[3-(2-ethoxyethoxy)propoxy]-1,4-dimethylbenzene,



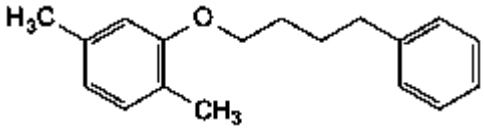
D. 5-[3,6-dimethyl-2-(prop-1-en-1-yl)phenoxy]-2,2-dimethylpentanoic acid,



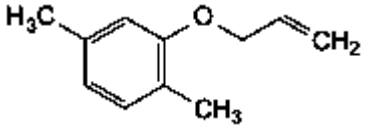
E. 5-[2,5-dimethyl-4-(prop-1-en-1-yl)phenoxy]-2,2-dimethylpentanoic acid,

www.webofpharma.com

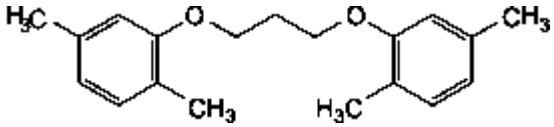
https://thuocngocanh.com/



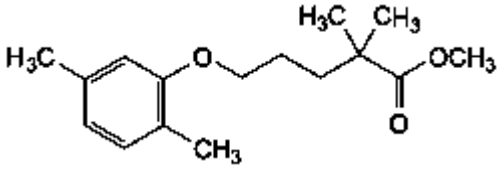
F. 1,4-dimethyl-2-(4-phenylbutoxy)benzene,



G. 1,4-dimethyl-2-(prop-2-en-1-yloxy)benzene,



H. 1,1′-[propane-1,3-diylbis(oxy)]bis(2,5-dimethylbenzene),



I. methyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gemfibrozil Capsules

General Notices

Action and use

Fibrate lipid-regulating drug.

DEFINITION

Gemfibrozil Capsules contain Gemfibrozil.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of gemfibrozil, $C_{15}H_{22}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the contents of the capsules containing about 0.5 g of Gemfibrozil with 10 mL of n-*hexane* for 10 minutes, filter through a filter paper previously washed with 20 mL of n-*hexane*, evaporate the filtrate to dryness on a water bath and then dry over *silica gel* at a pressure of 2 kPa for 2 hours or until a waxy solid is obtained. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of gemfibrozil *(RS 167)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.2M *phosphate buffer pH 7.5*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 276 nm, Appendix II B using 0.2M *phosphate buffer pH 7.5* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *gemfibrozil BPCRS,* adding the minimum volume of 0.1M *sodium hydroxide*, if necessary, to complete dissolution, and using 0.2M *phosphate buffer pH 7.5* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of gemfibrozil, $C_{15}H_{22}O_3$, in the medium from the absorbances obtained and using the declared content of $C_{15}H_{22}O_3$, in *gemfibrozil BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the contents of the capsules containing 0.4 g of Gemfibrozil with 100 mL of *methanol* and filter

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and further dilute 1 volume of this solution to 5 volumes with the mobile phase.

(3) 0.0004% w/v of *gemfibrozil impurity E BPCRS* in the mobile phase.

(4) 0.001% w/v of *gemfibrozil methyl ester BPCRS* and 0.0004% w/v of *gemfibrozil impurity E BPCRS* in solution (2).

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Assay may be used. For solution (1) allow the chromatography to proceed for twice the retention time of the principal peak.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to gemfibrozil and gemfibrozil methyl ester is at least 4.0 and the *resolution* between the peaks due to gemfibrozil methyl ester and gemfibrozil impurity E is at least 1.2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to gemfibrozil impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* other than any peak corresponding to gemfibrozil impurity E is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 50 mL of *methanol* to a quantity of the mixed contents of 20 capsules containing 0.15 g of Gemfibrozil, shake on a mechanical shaker for 10 minutes, add 20 mL of *water*, 1 mL of *glacial acetic acid* and sufficient *methanol* to produce 100 mL, mix and filter (Whatman GF/C paper is suitable), discarding the first 20 mL of filtrate. Dilute 1 volume of the filtrate to 5 volumes with the mobile phase.

(2) Dissolve 30 mg of *gemfibrozil BPCRS* in 80 mL of *methanol*, add 1 mL of *glacial acetic acid* and dilute to 100 mL with *water*.

(3) 0.01% w/v of *gemfibrozil methyl ester BPCRS* in a solution prepared by diluting 1 volume of solution (1) to 3 volumes with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS 2 or Regis C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 19 volumes of *water* and 80 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gemfibrozil and gemfibrozil methyl ester is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{22}O_3$ in the capsules from the chromatograms obtained using the declared content of $C_{15}H_{22}O_3$ in *gemfibrozil BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gemfibrozil Tablets

General Notices

Action and use

Fibrate lipid-regulating drug.

DEFINITION

Gemfibrozil Tablets contain Gemfibrozil.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of gemfibrozil, $C_{15}H_{22}O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix a quantity of the powdered tablets containing 0.3 g of Gemfibrozil with 10 mL of 0.1M *sodium hydroxide*, filter (Whatman 541 paper is suitable), acidify with a few drops of 2M *sulfuric acid*, shake and centrifuge. Wash the precipitate with *water*, allow to dry in air and dry over *anhydrous silica gel* at a pressure of 2 kPa for 4 hours. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of gemfibrozil *(RS 167)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.2M *phosphate buffer pH 7.5*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 276 nm, Appendix II B using 0.2M *phosphate buffer pH 7.5* in the reference cell.

(2) Measure the *absorbance* of a suitable solution of *gemfibrozil BPCRS* prepared by dissolving the substance in the minimum volume of *methanol* and diluting with 0.2M *phosphate buffer pH 7.5*. and using 0.2M *phosphate buffer pH 7.5* in the reference cell.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of gemfibrozil, $C_{15}H_{22}O_3$, in the medium from the absorbances obtained and using the declared content of $C_{15}H_{22}O_3$ in *gemfibrozil BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.6 g of Gemfibrozil with 70 mL of *methanol* for 15 minutes, add sufficient *methanol* to produce 100 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase and further dilute 1 volume of this solution to 5 volumes with mobile phase.
(3) 0.0006% w/v of *gemfibrozil impurity E BPCRS* in mobile phase.
(4) 0.001% w/v of *gemfibrozil methyl ester BPCRS* and 0.0004% w/v of *gemfibrozil impurity E BPCRS* in solution (2).

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Assay may be used. For solution (1) allow the chromatography to proceed for twice the retention time of the principal peak.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to gemfibrozil and gemfibrozil methyl ester is at least 4.0 and the *resolution* between the peaks due to gemfibrozil methyl ester and gemfibrozil impurity E is at least 1.2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to gemfibrozil impurity E is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* other than the peak corresponding to gemfibrozil impurity E is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 84 mg of Gemfibrozil with 80 mL of *methanol (80%)* on a mechanical shaker for 15 minutes, add sufficient *methanol (80%)* to produce 100 mL, mix and filter (Whatman 542 paper is suitable), discarding the first 20 mL of filtrate.
(2) 0.084% w/v of *gemfibrozil BPCRS* prepared by dissolving the substance in the minimum volume of *methanol* and diluting with *methanol (80%)*.

www.webofpharma.com

https://thuocngocanh.com/

(3) 0.01% w/v of *gemfibrozil methyl ester BPCRS* in a solution prepared by diluting 1 volume of solution (1) to 10 volumes with a mixture of 2 volumes of *methanol* and 3 volumes of mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Spherisorb ODS 2 or Regis C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 276 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 19 volumes of *water* and 80 volumes of *methanol*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gemfibrozil and gemfibrozil methyl ester is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{22}O_3$ in the tablets from the chromatograms obtained using the declared content of $C_{15}H_{22}O_3$ in *gemfibrozil BPCRS*.

STORAGE

Gemfibrozil Tablets should be protected from light.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gentamicin and Hydrocortisone Acetate Ear Drops

General Notices

Action and use

Aminoglycoside antibacterial (Gentamicin Sulfate); corticosteroid (Hydrocortisone Acetate).

DEFINITION

Gentamicin and Hydrocortisone Acetate Ear Drops contain Gentamicin Sulfate and Hydrocortisone Acetate suspended in a suitable vehicle.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

Content of hydrocortisone acetate, $C_{23}H_{32}O_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the ear drops, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.3% w/v of gentamicin, filter and use the filtrate.

(2) 0.5% w/v of *gentamicin sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution R1* and heat at 105° for 2 minutes.

MOBILE PHASE

The lower layer obtained by shaking together equal volumes of 13.5M *ammonia*, *dichloromethane* and *methanol* and allowing to separate.

CONFIRMATION

The three principal spots in the chromatogram obtained with solution (1) are similar in position, colour and size to those in the chromatogram obtained with solution (2).

B. Comply with the test for Composition of gentamicin sulfate.

C. Filter 20 mL of the well-mixed ear drops (Whatman No. 1 filter paper is suitable), wash the residue with the minimum amount of *water*, dry at 105° and dissolve 50 mg of the residue obtained in 50 mL of *ethanol (96%)*. Add 2 mL of *sulfuric acid* to 2 mL of the resulting

www.webofpharma.com

https://thuocngocanh.com/

solution; an intense yellow colour is produced which exhibits a green fluorescence which is particularly intense when viewed under *ultraviolet light (365 nm)*. Add the solution to 10 mL of *water* and mix; the fluorescence under *ultraviolet light (365 nm)* does not disappear.

D. In the Assay for hydrocortisone acetate, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 6.0 to 7.0, Appendix V L.

Composition of gentamicin sulfate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of *methanol* to 10 mL of a solution prepared by diluting a suitable volume of the ear drops with *water* to contain the equivalent of 0.045% w/v of gentamicin. Swirl and add 4 mL of *phthalaldehyde reagent*, mix and add sufficient *methanol* to produce 25 mL, heat in a water bath at 60° for 15 minutes and cool. If the solution is not used immediately, cool to 0° and use within 4 hours.

(2) Prepare in the same manner as solution (1) but using 10 mL of a 0.065% w/v solution of *gentamicin sulfate BPCRS* in place of 10 mL of the preparation being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS and Kromasil C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 330 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

0.025M *sodium heptanesulfonate monohydrate* in a mixture of 5 volumes of *glacial acetic acid*, 25 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of component C_2 is 10 to 20 minutes. The retention times relative to component C_2 are: about 0.13 (reagent); about 0.27 (component C_1); about 0.65 (component C_{1a}); about 0.85 (component C_{2a}).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to components C_{2a} and C_2 is at least 1.3.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

Using the chromatogram obtained with solution (1) calculate the percentage content of components C_1, C_{1a}, C_2 and C_{2a} in the ear drops by *normalisation*. The proportions are within the following limits:

C_1, 25.0 to 50.0%;

C_{1a}, 10.0 to 35.0%;

C_2 plus C_{2a}, 25.0 to 55.0%.

ASSAY

For gentamicin

Dilute a volume of the ear drops containing the equivalent of 15 mg of gentamicin to 50 mL with sterile *phosphate buffer pH 8.0* and dilute 10 mL of the resulting solution to 50 mL with the same solvent. Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

Calculate the content of gentamicin in the ear drops, taking each 1000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the stated content.

For hydrocortisone acetate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the ear drops containing 0.1 g of Hydrocortisone Acetate with 25 mL of *methanol*, add sufficient *methanol* to produce 100 mL and dilute 10 mL of this solution to 50 mL with the mobile phase.
(2) Dilute 10 mL of a 0.1% w/v solution of *hydrocortisone acetate BPCRS* in *methanol* to 50 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 256 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

400 volumes of *water* and 600 volumes of *methanol*.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{32}O_6$ in the ear drops using the declared content of $C_{23}H_{32}O_6$ in *hydrocortisone acetate BPCRS*.

STORAGE

www.webofpharma.com

https://thuocngocanh.com/

Gentamicin and Hydrocortisone Acetate Ear Drops should not be allowed to freeze.

LABELLING

The quantity of Gentamicin Sulfate is stated in terms of the equivalent amount of gentamicin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gentamicin Cream

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Gentamicin Cream is a viscous oil-in-water emulsion containing Gentamicin Sulfate dissolved in the aqueous phase.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the cream containing the equivalent of 7.5 mg of gentamicin in 20 mL of *chloroform*, extract with 10 mL of *water* and use the aqueous layer.

(2) A solution of *gentamicin sulfate BPCRS* in *water* containing the equivalent of 0.075% w/v of gentamicin.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution R1* and heat at 105° for 2 minutes.

MOBILE PHASE

The lower layer obtained by shaking together equal volumes of 13.5M *ammonia*, *chloroform* and *methanol* and allowing to separate.

CONFIRMATION

The three principal spots in the chromatogram obtained with solution (1) correspond to the three principal spots in the chromatogram obtained with solution (2).

B. In the test for Composition of gentamicin sulfate, the retention times of the four principal peaks in the chromatogram obtained with solution (1) correspond to those of the four principal peaks in the chromatogram obtained with solution (2).

TESTS

Composition of gentamicin sulfate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Disperse a quantity of the cream containing the equivalent of 15 mg of gentamicin in 10 mL of *chloroform*, add 10 mL of a 0.25% w/v solution of *sodium tetraborate*, shake vigorously, centrifuge and separate the aqueous layer. Repeat the extraction with two 5 mL quantities of the sodium tetraborate solution, dilute the combined aqueous extracts to 25 mL with the same solution and filter. To 10 mL of the clear filtrate add 5 mL of *methanol*, swirl, add 4 mL of *phthalaldehyde reagent*, mix, add sufficient *methanol* to produce 25 mL, heat in a water bath at 60° for 15 minutes and cool. If the solution is not used immediately, cool to 0° and use within 4 hours.

(2) Prepare in the same manner as solution (1) but using 10 mL of a 0.065% w/v solution of *gentamicin sulfate* *BPCRS* in place of the preparation being examined and beginning at the words 'To 10 mL of the clear filtrate …'.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS and Kromasil C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 330 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.025M *sodium heptanesulfonate monohydrate* in a mixture of 5 volumes of *glacial acetic acid*, 25 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of component C_2 is 10 to 20 minutes. The retention times relative to component C_2 are: about 0.13 (reagent); about 0.27 (component C_1); about 0.65 (component C_{1a}); about 0.85 (component C_{2a}).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to components C_{2a} and C_2 is at least 1.3.

LIMITS

Using the chromatogram obtained with solution (1) calculate the percentage content of components C_1, C_{1a}, C_2 and C_{2a} in the cream by *normalisation*. The proportions are within the following limits:

C_1, 25.0 to 50.0%;

C_{1a}, 10.0 to 35.0%;

C_2 plus C_{2a}, 25.0 to 55.0%.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve as completely as possible a quantity of the cream containing the equivalent of 3 mg of gentamicin in 20 mL of *chloroform*, shake vigorously with 75 mL of *phosphate buffer pH 8.0* and allow to separate. Dilute 10 mL of the aqueous layer to 50 mL with *phosphate buffer pH 8.0*. Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

Calculate the content of gentamicin in the cream, taking each 1000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the stated content.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of gentamicin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gentamicin Ear Drops

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Gentamicin Ear Drops are a solution of Gentamicin Sulfate in Purified Water.

The ear drops comply with the requirements stated under Ear Preparations and with the following requirements.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the ear drops, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.3% w/v of gentamicin.

(2) 0.5% w/v of *gentamicin sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution R1* and heat at 105° for 2 minutes.

MOBILE PHASE

The lower layer obtained by shaking together equal volumes of 13.5M *ammonia*, *chloroform* and *methanol* and allowing to separate.

CONFIRMATION

The three principal spots in the chromatogram obtained with solution (1) correspond to the three principal spots in the chromatogram obtained with solution (2).

B. In the test for Composition of gentamicin sulfate, the retention times of the four principal peaks in the chromatogram obtained with solution (1) correspond to those of the four principal peaks in the chromatogram obtained with solution (2).

TESTS

Composition of gentamicin sulfate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Add 5 mL of *methanol* to 10 mL of a solution prepared by diluting a suitable volume of the ear drops with *water* to contain the equivalent of 0.045% w/v of gentamicin. Swirl and add 4 mL of *phthalaldehyde reagent*, mix and add sufficient *methanol* to produce 25 mL, heat in a water bath at 60° for 15 minutes and cool. If the solution is not used immediately, cool to 0° and use within 4 hours.

(2) Prepare in the same manner as solution (1) but using 10 mL of a 0.065% w/v solution of *gentamicin sulfate* *BPCRS* in place of 10 mL of the preparation being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS and Kromasil C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 330 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.025M *sodium heptanesulfonate monohydrate* in a mixture of 5 volumes of *glacial acetic acid*, 25 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of component C_2 is 10 to 20 minutes. The retention times relative to component C_2 are: about 0.13 (reagent); about 0.27 (component C_1); about 0.65 (component C_{1a}); about 0.85 (component C_{2a}).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to components C_{2a} and C_2 is at least 1.3.

LIMITS

Using the chromatogram obtained with solution (1) calculate the percentage content of components C_1, C_{1a}, C_2 and C_{2a} in the ear drops by *normalisation*. The proportions are within the following limits:

C_1, 25.0 to 50.0%;

C_{1a}, 10.0 to 35.0%;

C_2 plus C_{2a}, 25.0 to 55.0%.

ASSAY

Dilute a volume of the ear drops containing the equivalent of 15 mg of gentamicin to 50 mL with sterile *phosphate buffer pH 8.0* and dilute 10 mL of the resulting solution to 50 mL with the same solvent. Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of gentamicin in the ear drops, taking each 1000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the stated content.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of gentamicin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gentamicin Eye Drops

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Gentamicin Eye Drops are a sterile solution of Gentamicin Sulfate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the eye drops, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.3% w/v of gentamicin.

(2) 0.5% w/v of *gentamicin sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution R1* and heat at 105° for 2 minutes.

MOBILE PHASE

The lower layer obtained by shaking together equal volumes of 13.5M *ammonia*, *chloroform* and *methanol* and allowing to separate.

CONFIRMATION

The three principal spots in the chromatogram obtained with solution (1) correspond to the three principal spots in the chromatogram obtained with solution (2).

B. In the test for Composition of gentamicin sulfate, the retention times of the four principal peaks in the chromatogram obtained with solution (1) correspond to those of the four principal peaks in the chromatogram obtained with solution (2).

TESTS

Composition of gentamicin sulfate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

www.webofpharma.com

https://thuocngocanh.com/

(1) Add 5 mL of *methanol* to 10 mL of a solution prepared by diluting a suitable volume of the eye drops with *water* to contain the equivalent of 0.045% w/v of gentamicin. Swirl and add 4 mL of *phthalaldehyde reagent*, mix and add sufficient *methanol* to produce 25 mL, heat in a water bath at 60° for 15 minutes and cool. If the solution is not used immediately, cool to 0° and use within 4 hours.

(2) Prepare in the same manner as solution (1) but using 10 mL of a 0.065% w/v solution of *gentamicin sulfate* *BPCRS* in place of 10 mL of the preparation being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS and Kromasil C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 330 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.025M *sodium heptanesulfonate monohydrate* in a mixture of 5 volumes of *glacial acetic acid*, 25 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of component C_2 is 10 to 20 minutes. The retention times relative to component C_2 are: about 0.13 (reagent); about 0.27 (component C_1); about 0.65 (component C_{1a}); about 0.85 (component C_{2a}).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to components C_{2a} and C_2 is at least 1.3.

LIMITS

Using the chromatogram obtained with solution (1) calculate the percentage content of components C_1, C_{1a}, C_2 and C_{2a} in the eye drops by *normalisation*. The proportions are within the following limits:

C_1, 25.0 to 50.0%;

C_{1a}, 10.0 to 35.0%;

C_2 plus C_{2a}, 25.0 to 55.0%.

ASSAY

Dilute a volume of the eye drops containing the equivalent of 15 mg of gentamicin to 50 mL with sterile *phosphate buffer pH 8.0* and dilute 10 mL of the resulting solution to 50 mL with the same solvent. Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

www.webofpharma.com

https://thuocngocanh.com/

Calculate the content of gentamicin in the eye drops, taking each 1000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the stated content.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of gentamicin.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gentamicin Injection

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Gentamicin Injection is a sterile solution of Gentamicin Sulfate in Water for Injections.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the injection, if necessary, with sufficient *water* to produce a solution containing the equivalent of 0.5% w/v of gentamicin.

(2) 0.8% w/v of *gentamicin sulfate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 6 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution R1* and heat at 105° for 2 minutes.

MOBILE PHASE

The lower layer obtained by shaking together equal volumes of 13.5M *ammonia*, *chloroform* and *methanol* and allowing to separate.

CONFIRMATION

The three principal spots in the chromatogram obtained with solution (1) correspond to the three principal spots in the chromatogram obtained with solution (2).

B. In the test for Composition of gentamicin sulfate, the retention times of the four principal peaks in the chromatogram obtained with solution (1) correspond to those of the four principal peaks in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 3.0 to 5.5, Appendix V L.

www.webofpharma.com

https://thuocngocanh.com/

Composition of gentamicin sulfate

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 5 mL of *methanol* to 10 mL of a solution prepared by diluting a suitable volume of the injection with *water* to contain the equivalent of 0.045% w/v of gentamicin. Swirl and add 4 mL of *phthalaldehyde reagent*, mix and add sufficient *methanol* to produce 25 mL, heat in a water bath at 60° for 15 minutes and cool. If the solution is not used immediately, cool to 0° and use within 4 hours.

(2) Prepare in the same manner as solution (1) but using 10 mL of a 0.065% w/v solution of *gentamicin sulfate BPCRS* in place of 10 mL of the preparation being examined.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS and Kromasil C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 330 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.025M *sodium heptanesulfonate monohydrate* in a mixture of 5 volumes of *glacial acetic acid*, 25 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of component C_2 is 10 to 20 minutes. The retention times relative to component C_2 are: about 0.13 (reagent); about 0.27 (component C_1); about 0.65 (component C_{1a}); about 0.85 (component C_{2a}).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to components C_{2a} and C_2 is at least 1.3.

LIMITS

Using the chromatogram obtained with solution (1) calculate the percentage content of components C_1, C_{1a}, C_2 and C_{2a} in the injection by *normalisation*. The proportions are within the following limits:

C_1, 25.0 to 50.0%;

C_{1a}, 10.0 to 35.0%;

C_2 plus C_{2a}, 25.0 to 55.0%.

Bacterial endotoxins

www.webofpharma.com

https://thuocngocanh.com/

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dilute the injection, if necessary, with *water BET* to give a solution containing the equivalent of 10 mg of gentamicin per mL (solution A). The endotoxin limit concentration of solution A is 7.1 IU per mL.

ASSAY

Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

Calculate the content of gentamicin in the injection, taking each 1000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated content.

LABELLING

The strength is stated in terms of the equivalent amount of gentamicin in a suitable dose-volume.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gentamicin Ointment

General Notices

Action and use

Aminoglycoside antibacterial.

DEFINITION

Gentamicin Ointment is a dispersion of Gentamicin Sulfate in *microfine powder* in White Soft Paraffin or other suitable anhydrous greasy basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Disperse a quantity of the ointment containing the equivalent of 7.5 mg of gentamicin in 20 mL of *chloroform*, extract with 10 mL of *water* and use the aqueous layer.

(2) A solution of *gentamicin sulfate BPCRS* in *water* containing the equivalent of 0.075% w/v of gentamicin.

CHROMATOGRAPHIC CONDITIONS

(a) Use a silica gel precoated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air, spray with *ninhydrin solution R1* and heat at 105° for 2 minutes.

MOBILE PHASE

The lower layer obtained by shaking together equal volumes of 13.5M *ammonia*, *chloroform* and *methanol* and allowing to separate.

CONFIRMATION

The three principal spots in the chromatogram obtained with solution (1) correspond to the three principal spots in the chromatogram obtained with solution (2).

B. In the test for Composition of gentamicin sulfate, the retention times of the four principal peaks in the chromatogram obtained with solution (1) correspond to those of the four principal peaks in the chromatogram obtained with solution (2).

TESTS

Composition of gentamicin sulfate

www.webofpharma.com

https://thuocngocanh.com/

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the ointment containing the equivalent of 20 mg of gentamicin in 10 mL of *chloroform*, add 20 mL of a 0.25% w/v solution of *sodium tetraborate*, shake vigorously, centrifuge and separate the aqueous layer. Filter and dilute to 50 mL with *water*. To 10 mL add 5 mL of *methanol*, swirl, add 4 mL of *phthalaldehyde reagent*, mix, add sufficient *methanol* to produce 25 mL, heat in a water bath at 60° for 15 minutes and cool. If the solution is not to be used immediately, cool to 0° and use within 4 hours

(2) Prepare in the same manner as solution (1) but using 10 mL of a 0.065% w/v solution of *gentamicin sulfate* *BPCRS* in place of the preparation being examined and beginning at the words 'To 10 mL add …'.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS and Kromasil C18 are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 330 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

0.025M *sodium heptanesulfonate monohydrate* in a mixture of 5 volumes of *glacial acetic acid*, 25 volumes of *water* and 70 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of component C_2 is 10 to 20 minutes. The retention times relative to component C_2 are: about 0.13 (reagent); about 0.27 (component C_1); about 0.65 (component C_{1a}); about 0.85 (component C_{2a}).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution factor* between the peaks due to components C_{2a} and C_2 is at least 1.3.

LIMITS

Using the chromatogram obtained with solution (1) calculate the percentage content of components C_1, C_{1a}, C_2 and C_{2a} in the ointment by *normalisation*. The proportions are within the following limits:

C_1, 25.0 to 50.0%;

C_{1a}, 10.0 to 35.0%;

C_2 plus C_{2a}, 25.0 to 55.0%.

ASSAY

www.webofpharma.com

https://thuocngocanh.com/

Dissolve as completely as possible a quantity of the ointment containing the equivalent of 4 mg of gentamicin in 50 mL of *chloroform*, extract with three 20-mL quantities of *phosphate buffer pH 8.0* and dilute the combined extracts to 100 mL with *phosphate buffer pH 8.0*. Dilute 10 mL of the resulting solution to 50 mL with *phosphate buffer pH 8.0*. Carry out the *microbiological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency.

Calculate the content of gentamicin in the ointment, taking each 1000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 120.0% of the stated content.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of gentamicin.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

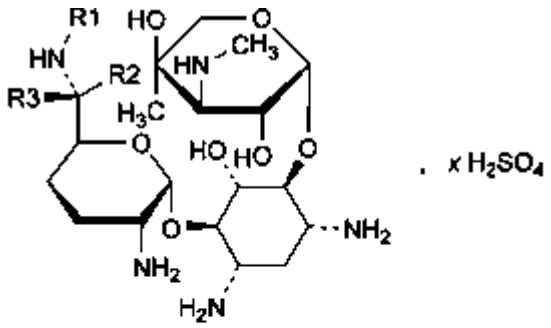
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gentamicin Sulfate

General Notices

(Ph. Eur. monograph 0331)



Gentamicin	Mol. Formula	R1	R2	R3
C1	$C_{21}H_{43}N_5O_7$	CH_3	CH_3	H
C1a	$C_{19}H_{39}N_5O_7$	H	H	H
C2	$C_{20}H_{41}N_5O_7$	H	CH_3	H
C2a	$C_{20}H_{41}N_5O_7$	H	H	CH_3
C2b	$C_{20}H_{41}N_5O_7$	CH_3	H	H

1405-41-0

Action and use

Aminoglycoside antibacterial.

Preparations

Gentamicin Cream

Gentamicin Ear Drops

Gentamicin and Hydrocortisone Acetate Ear Drops

Gentamicin Eye Drops

Gentamicin Injection

Gentamicin Ointment

Ph Eur

DEFINITION

www.webofpharma.com

https://thuocngocanh.com/

Mixture of the sulfates of antimicrobial substances produced by *Micromonospora purpurea*, the main components being gentamicins C1, C1a, C2, C2a and C2b.

Content

Minimum 590 IU/mg (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, C.

Second identification: A, C.

A. Thin-layer chromatography (2.2.27).

Test solution Dissolve 25 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution Dissolve the contents of a vial of *gentamicin sulfate CRS* in *water R* and dilute to 5 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase The lower layer of a mixture of equal volumes of *concentrated ammonia R*, *methanol R* and *methylene chloride R*.

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ninhydrin solution R1* and heat at 110 °C for 5 min.

Results The 3 principal spots in the chromatogram obtained with the test solution are similar in position, colour and size to the 3 principal spots in the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the test for composition.

Results The chromatogram obtained with test solution (b) shows 5 principal peaks having the same retention times as the 5 principal peaks in the chromatogram obtained with reference solution (a).

C. It gives reaction (a) of sulfates (2.3.1).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Solution S

Dissolve 0.8 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

pH (*2.2.3*)

3.5 to 5.5 for solution S.

Specific optical rotation (*2.2.7*)

+ 107 to + 121 (anhydrous substance).

Dissolve 2.5 g in *water R* and dilute to 25.0 mL with the same solvent.

Composition

Liquid chromatography (*2.2.29*): use the normalisation procedure taking into account only the peaks due to gentamicins C1, C1a, C2, C2a and C2b.

Test solution (a) Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Test solution (b) Dilute 5.0 mL of test solution (a) to 25.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *gentamicin for peak identification CRS* (containing impurity B) in the mobile phase and dilute to 25 mL with the mobile phase.

Reference solution (b) Dissolve 20.0 mg of *sisomicin sulfate CRS* (impurity A) in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 100.0 mL with the mobile phase.

Reference solution (d) To 1 mL of reference solution (b), add 5 mL of test solution (a) and dilute to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 35 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase To 900 mL of *carbon dioxide-free water R*, add 7.0 mL of *trifluoroacetic acid R*, 250.0 µL of *pentafluoropropanoic acid R* and 4.0 mL of *carbonate-free sodium hydroxide solution R*, allow to equilibrate and adjust to pH 2.6 using *carbonate-free sodium hydroxide solution R* diluted 1 to 25. Add 15 mL of *acetonitrile R* and dilute to 1000.0 mL with *carbon dioxide-free water R*.

Flow rate 1.0 mL/min.

Post-column solution *carbonate-free sodium hydroxide solution R* diluted 1 to 25, previously degassed, which is added pulse-less to the column effluent using a 375 µL polymeric mixing coil.

Flow rate of post-column solution 0.3 mL/min.

Detection Pulsed amperometric detector or equivalent with a gold indicator electrode, a silver-silver chloride reference electrode, and a stainless steel auxiliary electrode which is the cell body, held at respectively + 0.05 V detection, + 0.75 V oxidation and -0.15 V reduction potentials, with pulse durations according to the instrument used.

Injection 20 µL of test solution (b) and reference solutions (a), (c) and (d).

Run time 1.2 times the retention time of gentamicin C1.

Identification of peaks Use the chromatogram supplied with *gentamicin for peak identification CRS* to identify the peaks due to gentamicins C1, C1a, C2, C2a and C2b.

Relative retention With reference to impurity A (retention time = about 23 min): gentamicin C1a = about 1.1; gentamicin C2 = about 1.8; gentamicin C2b = about 2.0; gentamicin C2a = about 2.3; gentamicin C1 = about 3.0.

System suitability:

— *resolution*: minimum 1.2 between the peaks due to impurity A and gentamicin C1a and minimum 1.5 between the peaks due to gentamicin C2 and gentamicin C2b in the chromatogram obtained with reference solution (d); if necessary, adjust the volume of *acetonitrile R* in the mobile phase, a total volume of up to 50 mL may be added per litre of mobile phase;

— *signal-to-noise ratio*: minimum 20 for the principal peak in the chromatogram obtained with reference solution (c).

Limits:

— *gentamicin C1*: 25.0 per cent to 45.0 per cent;

— *gentamicin C1a*: 10.0 per cent to 30.0 per cent;

— *sum of gentamicins C2, C2a and C2b*: 35.0 per cent to 55.0 per cent.

Related substances

Liquid chromatography (*2.2.29*) as described in the test for composition with the following modifications; use reference solution (c) to calculate the percentage content of each impurity.

Injection 20 µL of test solution (a) and reference solutions (a) and (c).

www.webofpharma.com

https://thuocngocanh.com/

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram supplied with *gentamicin for peak identification CRS* and the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Limits:

— *impurities A, B*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 per cent);

— *any other impurity*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (10 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent).

Methanol (*2.4.24, System B*)

Maximum 1.0 per cent.

Sulfate

32.0 per cent to 35.0 per cent (anhydrous substance).

Dissolve 0.250 g in 100 mL of *distilled water R* and adjust the solution to pH 11 using *concentrated ammonia R*. Add 10.0 mL of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate*, adding 50 mL of *ethanol (96 per cent) R* when the colour of the solution begins to change and continue the titration until the violet-blue colour disappears.

1 mL of *0.1 M barium chloride* is equivalent to 9.606 mg of SO_4.

Water (*2.5.12*)

Maximum 15.0 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 0.50 g.

Bacterial endotoxins (*2.6.14*)

Less than 0.71 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*). Use *gentamicin sulfate CRS* as the chemical reference substance.

STORAGE

www.webofpharma.com

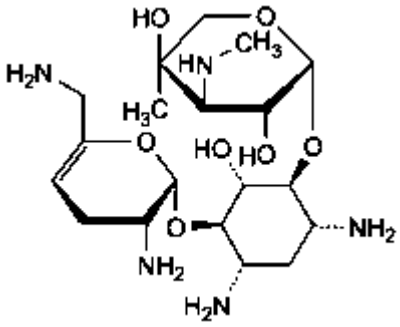
https://thuocngocanh.com/

In an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

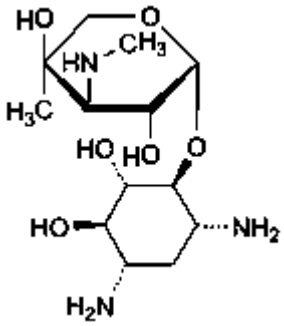
IMPURITIES

Specified impurities A, B.

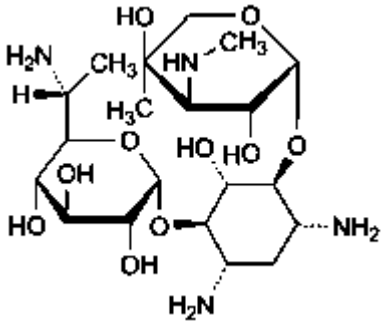
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C, D, E.



A. 2-deoxy-4-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-6-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-4-enopyranosyl)-L-streptamine (sisomicin),



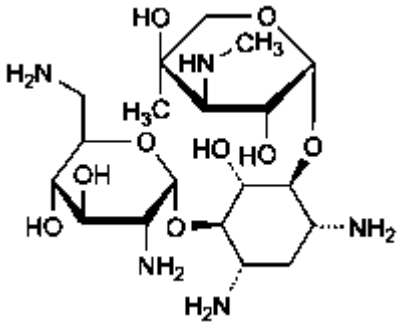
B. 2-deoxy-4-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-L-streptamine (garamine),



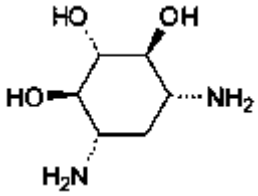
C. 4-*O*-(6-amino-6,7-dideoxy-D-*glycero*-α-D-*gluco*-heptopyranosyl)-2-deoxy-6-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-D-streptamine (gentamicin B_1),

www.webofpharma.com

https://thuocngocanh.com/



D. 2-deoxy-4-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl]-6-*O*-(2,6-diamino-2,6-dideoxy-α-D-*gluco*-hexopyranosyl)-L-streptamine,



E. 2-deoxystreptamine.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

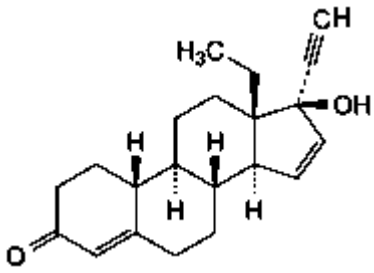
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gestodene

General Notices

(Ph. Eur. monograph 1726)



$C_{21}H_{26}O_2$ 310.4 *60282-87-3*

Action and use

Progestogen.

Ph Eur

DEFINITION

13-Ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Specific optical rotation (see Tests).

www.webofpharma.com

https://thuocngocanh.com/

B. Infrared absorption spectrophotometry (2.2.24).

Comparison gestodene CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in acetone R, evaporate to dryness and record new spectra using the residues.

TESTS

Specific optical rotation (2.2.7)

-188 to -198 (dried substance).

Dissolve 0.100 g in methanol R and dilute to 10.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, water R (50:50 *V/V*).

Test solution (a) Dissolve 30.0 mg of the substance to be examined in 5 mL of acetonitrile R1 and dilute to 10.0 mL with water R.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

Reference solution (a) Dissolve 3 mg of gestodene for system suitability CRS (containing impurities A, B, C and L) in 0.5 mL of acetonitrile R1 and dilute to 1.0 mL with water R.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 30.0 mg of gestodene CRS in 5 mL of acetonitrile R1 and dilute to 10.0 mL with water R. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (d) Dissolve the contents of a vial of gestodene impurity I CRS in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical end-capped octylsilyl silica gel for chromatography R (3.5 µm).

Mobile phase:

— *mobile phase A*: water R;

— *mobile phase B*: acetonitrile R1;

www.webofpharma.com

https://thuocngocanh.com/

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	62	38
2 - 20	62 → 58	38 → 42
20 - 24	58 → 30	42 → 70
24 - 32	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 205 nm and at 254 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (d).

Identification of impurities Use the chromatogram supplied with *gestodene for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and L; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity I.

Relative retention With reference to gestodene (retention time = about 12.5 min): impurity A = about 0.9; impurity C = about 1.1; impurity I = about 1.2; impurity L = about 1.46; impurity B = about 1.53.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurity A and gestodene.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.2; impurity I = 1.3;

— *impurity A at 254 nm*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity B at 205 nm*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity C at 254 nm*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurities I, L at 205 nm*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities at 254 nm*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *total at 254 nm*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit at 254 nm*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (c).

Detection Spectrophotometer at 254 nm.

Calculate the percentage content of $C_{21}H_{26}O_2$ from the declared content of *gestodene CRS*.

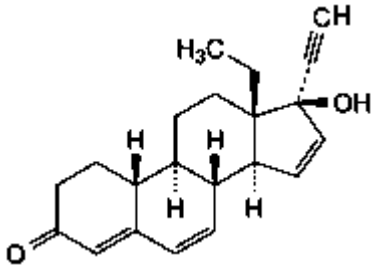
IMPURITIES

Specified impurities *A, B, C, I, L.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use)

— *at 205 nm*: *G, J, K*;

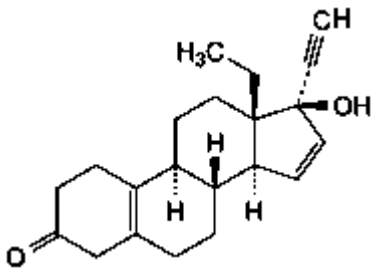
— *at 254 nm*: *D, E, F, H*.



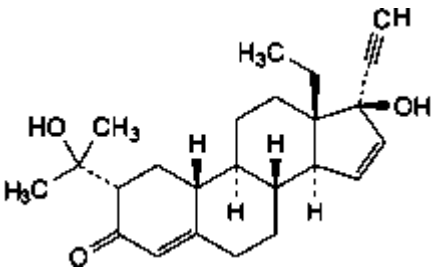
A. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,6,15-trien-20-yn-3-one (Δ6-gestodene),

www.webofpharma.com

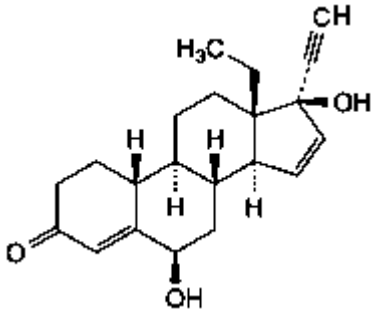
https://thuocngocanh.com/



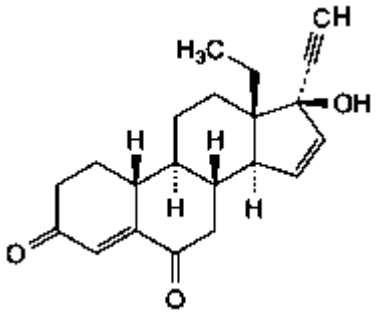
B. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-5(10),15-dien-20-yn-3-one (Δ5(10)-gestodene),



C. 13-ethyl-17-hydroxy-2α-(1-hydroxy-1-methylethyl)-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one (2-isopropanol-gestodene),



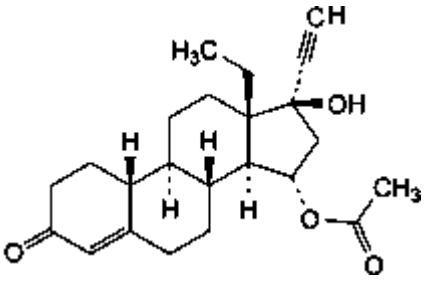
D. 13-ethyl-6β,17-dihydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one (6β-hydroxy-gestodene),



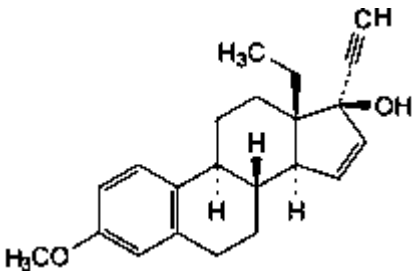
E. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yne-3,6-dione (6-keto-gestodene),

www.webofpharma.com

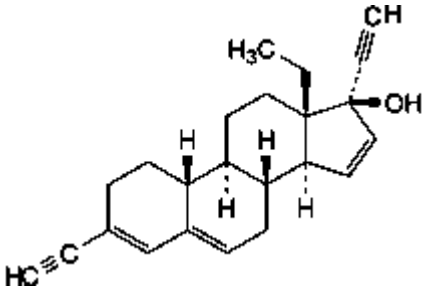
https://thuocngocanh.com/



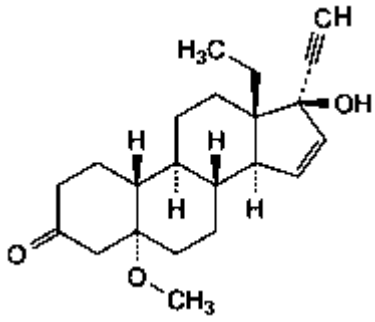
F. 13-ethyl-17-hydroxy-3-oxo-18,19-dinor-17α-pregn-4-en-20-yn-15α-yl acetate (15α-acetoxy-gestodene),



G. 13-ethyl-3-methoxy-18,19-dinor-17α-pregna-1,3,5(10),15-tetraen-20-yn-17-o1 (*A*-aromatic-gestodene),



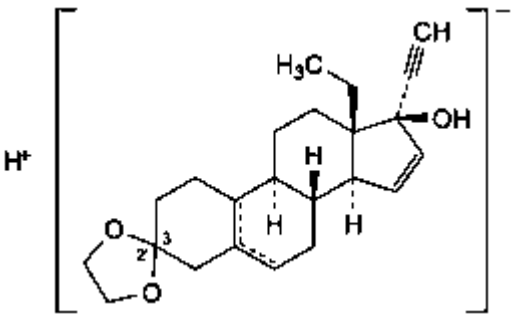
H. 13-ethyl-3-ethynyl-18,19-dinor-17α-pregna-3,5,15-trien-20-yn-17-o1 (diethynyl-gestodene),



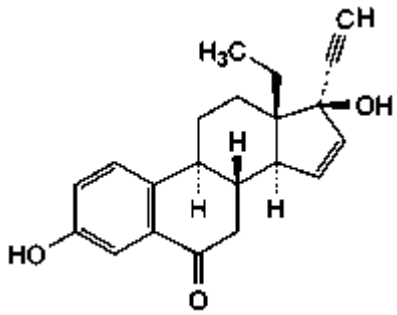
I. 13-ethyl-17-hydroxy-5-methoxy-18,19-dinor-5α,17α-pregn-15-en-20-yn-3-one (5-methoxy-gestodene),

www.webofpharma.com

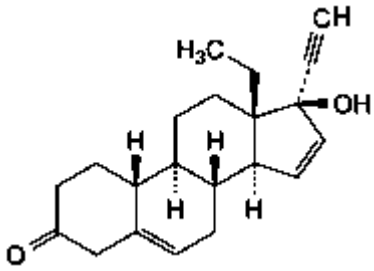
https://thuocngocanh.com/



J. 13-ethylspiro(18,19-dinor-17α-pregna-5,15-dien-20-yne-3,2′-[1,3]dioxolan)-17-ol and 13-ethylspiro(18,19-dinor-17α-pregna-5(10),15-dien-20-yne-3,2′-[1,3]dioxolan)-17-ol (gestodene ketal),



K. 13-ethyl-3,17-dihydroxy-18,19-dinor-17α-pregna-1,3,5(10),15-tetraen-20-yn-6-one (aromatic 6-keto-gestodene),



L. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-5,15-dien-20-yn-3-one (Δ5(6)-gestodene).

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

www.webofpharma.com

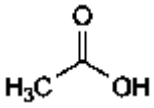
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glacial Acetic Acid

General Notices

(Ph. Eur. monograph 0590)



$C_2H_4O_2$ 60.1 *64-19-7*

Ph Eur

DEFINITION

Content

99.0 per cent *m/m* to 100.5 per cent *m/m*.

CHARACTERS

Appearance

Crystalline mass or clear, colourless, volatile liquid.

Solubility

Miscible with water, with ethanol (96 per cent) and with methylene chloride.

IDENTIFICATION

A. A 100 g/L solution is strongly acid (2.2.4).

B. To 0.03 mL add 3 mL of *water R* and neutralise with *dilute sodium hydroxide solution R*. The solution gives reaction (b) of acetates (2.3.1).

TESTS

Solution S

Dilute 20 mL to 100 mL with *distilled water R*.

Appearance

www.webofpharma.com

https://thuocngocanh.com/

The substance to be examined is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Freezing point (*2.2.18*)

Minimum 14.8 °C.

Reducing substances

Dilute 2.0 mL to 10.0 mL with *water R*. Add 0.1 mL of *0.02 M potassium permanganate*. Heat on a water-bath for 1 min, the colour remains pink.

Chlorides (*2.4.4*)

Maximum 25 mg/L.

Dilute 10 mL of solution S to 15 mL with *water R*.

Sulfates (*2.4.13*)

Maximum 50 mg/L, determined on solution S.

Iron (*2.4.9*)

Maximum 5 ppm.

Dissolve the residue obtained in the test for residue on evaporation by heating with 2 quantities, each of 15 mL, of *water R* and dilute to 50.0 mL with *water R*. Dilute 5.0 mL of the solution to 10.0 mL with *water R*.

Residue on evaporation

Maximum 0.01 per cent.

Evaporate 20 g to dryness on a water-bath and dry at 100-105 °C. The residue weighs a maximum of 2.0 mg.

ASSAY

Weigh accurately a conical flask with a ground-glass stopper containing 25 mL of *water R*. Add 1.0 mL of the substance to be examined and weigh again accurately. Add 0.5 mL of *phenolphthalein solution R* and titrate with *1 M sodium hydroxide*.

1 mL of *1 M sodium hydroxide* is equivalent to 60.1 mg of $C_2H_4O_2$.

STORAGE

In an airtight container.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

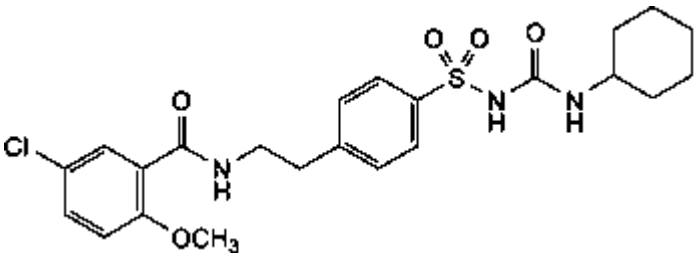
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glibenclamide

General Notices

(Ph. Eur. monograph 0718)



$C_{23}H_{28}ClN_3O_5S$ 494.0 *10238-21-8*

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

Preparation

Glibenclamide Tablets

Ph Eur

DEFINITION

1-[[4-[2-[(5-Chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]-3-cyclohexylurea.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent) and in methanol.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: C.

Second identification: A, B, D, E.

A. Melting point (2.2.14): 169 °C to 174 °C.

B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in methanol R, with the aid of ultrasound if necessary, and dilute to 50.0 mL with the same solvent. To 10.0 mL of the solution add 1.0 mL of a 103 g/L solution of hydrochloric acid R and dilute to 100.0 mL with methanol R.

Spectral range 230-350 nm.

Absorption maxima At 300 nm and a less intense maximum at 275 nm.

Specific absorbance at the absorption maxima:

— at 300 nm: 61 to 65;

— at 275 nm: 27 to 32.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison glibenclamide CRS.

If the spectra obtained show differences, moisten separately the substance to be examined and the reference substance with methanol R, triturate, dry at 100-105 °C and record the spectra again.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 10 mL with the same mixture of solvents.

Reference solution Dissolve 10 mg of glibenclamide CRS in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 10 mL with the same mixture of solvents.

Plate TLC silica gel GF_{254} plate R.

Mobile phase ethanol (96 per cent) R, glacial acetic acid R, cyclohexane R, methylene chloride R (5:5:45:45 *V/V/V/V*).

Application 10 µL.

Development Over 1/2 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

www.webofpharma.com

https://thuocngocanh.com/

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

E. Dissolve 20 mg in 2 mL of *sulfuric acid R*. The solution is colourless and shows blue fluorescence in ultraviolet light at 365 nm. Dissolve 0.1 g of *chloral hydrate R* in the solution. After about 5 min, the colour changes to deep yellow and, after about 20 min, develops a brownish tinge.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or store them at 5 °C for not more than 40 h.*

Test solution Dissolve 25.0 mg of the substance to be examined in *methanol R*, with the aid of ultrasound if necessary, and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 3.0 mg of *glibenclamide impurity A CRS* and 3 mg of *glibenclamide impurity B CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 20.0 mL with *methanol R*.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 12.5 mg of *glibenclamide for peak identification CRS* (containing impurity C) in *methanol R*, with the aid of ultrasound if necessary, and dilute to 5.0 mL with the same solvent.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: spherical *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 20 mL of a 100.0 g/L solution of *triethylamine R2* previously adjusted to pH 3.0 using *phosphoric acid R*, and 50 mL of *acetonitrile R*; dilute to 1000 mL with *water R*;

— *mobile phase B*: mobile phase A, *water R*, *acetonitrile R* (2:6.5:91.5 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	45	55
15 - 30	45 → 5	55 → 95
30 - 40	5	95

www.webofpharma.com

https://thuocngocanh.com/

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A and B; use the chromatogram supplied with *glibenclamide for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity C.

Relative retention With reference to glibenclamide (retention time = about 5 min): impurity A = about 0.5; impurity B = about 0.6; impurity C = about 0.7.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities A and B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.8;

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: 0.8 per cent;

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g with heating in 100 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 49.40 mg of $C_{23}H_{28}ClN_3O_5S$.

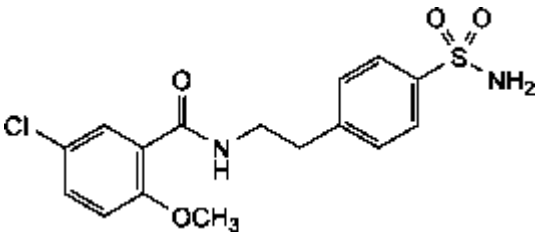
www.webofpharma.com

https://thuvienthuocngocanh.com/

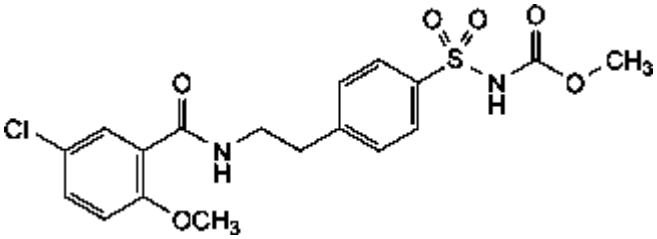
IMPURITIES

Specified impurities *A, C.*

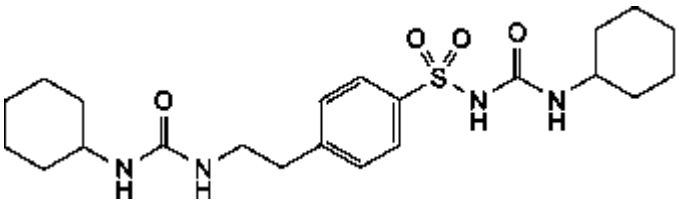
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, D, E.*



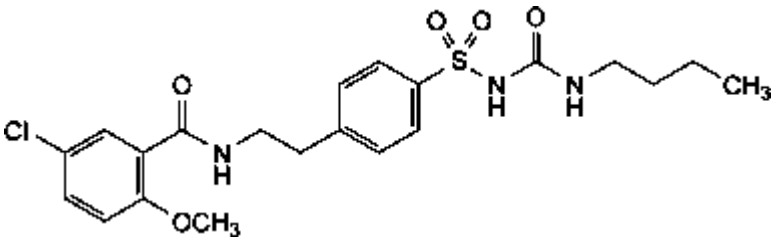
A. 5-chloro-2-methoxy-*N*-[2-(4-sulfamoylphenyl)ethyl]benzamide,



B. methyl [[4-[2-[(5-chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]carbamate,



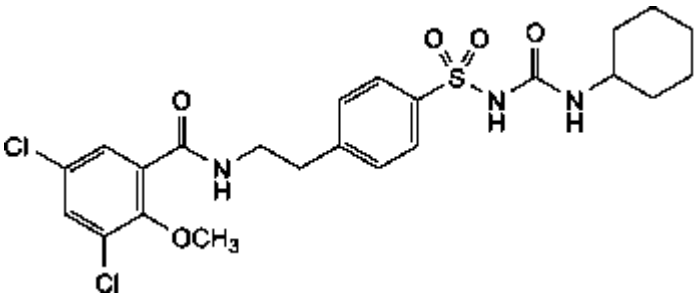
C. 1-cyclohexyl-3-[[4-[2-[(cyclohexylcarbamoyl)amino]ethyl]phenyl]sulfonyl]urea,



D. 1-butyl-3-[[4-[2-[(5-chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]urea,

www.webofpharma.com

https://thuocngocanh.com/



E. 1-cyclohexyl-3-[[4-[2-[(3,5-dichloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]urea.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glibenclamide Tablets

General Notices

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

DEFINITION

Glibenclamide Tablets contain Glibenclamide.

PRODUCTION

The dissolution test below is carried out to demonstrate the appropriate release of Glibenclamide subject to approval from the competent authority.

Prepare a mixture containing 0.8134% w/v of *anhydrous disodium hydrogen phosphate* and 0.1350% w/v of *potassium dihydrogen orthophosphate* (solution A).

Carry out the *dissolution test for tablets and capsules*, Appendix XII B1. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

TEST CONDITIONS

(a) Use Apparatus 2 rotating the paddle at 100 revolutions per minute.
(b) Use 900 mL of solution A at a temperature of 37° as the medium.

PROCEDURE

(1) Withdraw 10 mL of the medium, filter (Minisart GS 25mm filters are suitable) and use the filtrate, discarding the first 5 mL of the filtrate.
(2) Dissolve *glibenclamide BPCRS* in the minimum quantity of *methanol* and dilute to an appropriate concentration with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS is suitable).
(b) Use isocratic elution using the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

www.webofpharma.com

https://thuocngocanh.com/

40 volumes of 0.1M *potassium dihydrogen orthophosphate* previously adjusted to pH 3.0 with *orthophosphoric acid* and 60 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the total content of glibenclamide, $C_{23}H_{28}ClN_3O_5S$, in the medium from the chromatograms obtained and using the declared content of $C_{23}H_{28}ClN_3O_5S$ in *glibenclamide BPCRS*.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of glibenclamide, $C_{23}H_{28}ClN_3O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (4).

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing 20 mg of Glibenclamide with four 5-mL quantities of a mixture of 10 volumes of *acetone* and 20 volumes of *dichloromethane*, evaporate the combined extracts to dryness at a temperature not exceeding 40° at a pressure of 2 kPa and dissolve the residue in 4 mL of a mixture of equal volumes of *chloroform* and *methanol*.

(2) 0.012% w/v of *4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonamide BPCRS* in a mixture of equal volumes of *chloroform* and *methanol*.

(3) 0.0020% w/v of *methyl* N-*4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonylcarbamate BPCRS* in a mixture of equal volumes of *chloroform* and *methanol*.

(4) 0.5% w/v of *glibenclamide BPCRS* in a mixture of equal volumes of *chloroform* and *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating substance *silica gel* GF_{254}.

(b) Use the mobile phase described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *ethanol (96%)*, 5 volumes of *glacial acetic acid*, 45 volumes of *chloroform* and 45 volumes of *cyclohexane*.

www.webofpharma.com

https://thuocngocanh.com/

LIMITS

In the chromatogram obtained with solution (1);

any spots corresponding to 4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonamide and methyl *N*-4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonylcarbamate are not more intense than the spots in the chromatograms obtained with solutions (2) (2.4%) and (3)(0.4%) respectively.

Uniformity of content

Tablets containing 5 mg or less of Glibenclamide comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Powder one tablet, add a mixture of 2 mL of *water* and 20 mL of *methanol*, mix with the aid of ultrasound until fully dispersed and filter through a 0.2-µm membrane filter (Anatop LC is suitable).
(2) Add 2 mL of *water* to 20 mL of a 0.025% w/v solution of *glibenclamide BPCRS* in *methanol*, mix with the aid of ultrasound until fully dispersed and filter (0.2-µm Anatop LC is suitable).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{28}ClN_3O_5S$ in each tablet using the declared content of $C_{23}H_{28}ClN_3O_5S$ in *glibenclamide BPCRS*.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound, a quantity of the powdered tablets containing 5 mg of Glibenclamide with a mixture of 2 mL of *water* and 20 mL of *methanol* until fully dispersed and filter through a 0.2-µm membrane filter (Anatop LC is suitable).
(2) Dissolve 50 mg of *glibenclamide BPCRS* in 10 mL of *methanol* with the aid of ultrasound for 20 minutes, add sufficient *methanol* to produce 50 mL and dilute 1 volume of this solution to 4 volumes with *methanol*. To 20 mL of this solution add 2 mL of *water* and mix.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS is suitable).
(b) Use isocratic elution using the mobile phase below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 300 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

47 volumes of *acetonitrile* and 53 volumes of a 1.36% w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 3.0 with *orthophosphoric acid*.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{28}ClN_3O_5S$ in the tablets using the declared content of $C_{23}H_{28}ClN_3O_5S$ in *glibenclamide BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

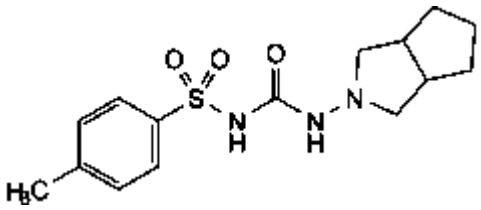
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gliclazide

General Notices

(Ph. Eur. monograph 1524)



$C_{15}H_{21}N_3O_3S$ 323.4 *21187-98-4*

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

Preparation

Gliclazide Tablets

Ph Eur

DEFINITION

N-[(Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)carbamoyl]-4-methylbenzene-1-sulfonamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *gliclazide CRS*.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture *acetonitrile R*, *water R* (45:55 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 23 mL of *acetonitrile R* and dilute to 50.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 10.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 15 mg of *gliclazide impurity F CRS* in 23 mL of *acetonitrile R* and dilute to 50 mL with *water R*. Dilute 1 mL of the solution to 20 mL with the solvent mixture.

Reference solution (c) Dissolve 15.0 mg of *gliclazide impurity F CRS* in 45 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (4 µm).

Mobile phase *triethylamine R*, *trifluoroacetic acid R*, *acetonitrile for chromatography R*, *water for chromatography R* (0.1:0.1:45:55 *V/V/V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 235 nm.

Injection 20 µL.

Run time Twice the retention time of gliclazide.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity F.

Relative retention With reference to gliclazide (retention time = about 16 min): impurity F = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 1.8 between the peaks due to impurity F and gliclazide.

Limits:

— *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than F*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurity B

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Test solution Dissolve 0.400 g of the substance to be examined in 2.5 mL of *dimethyl sulfoxide R* and dilute to 10.0 mL with *water R*. Stir for 10 min, store at 4 °C for 30 min and filter.

Reference solution Dissolve 20.0 mg of *gliclazide impurity B CRS* in *dimethyl sulfoxide R* and dilute to 100.0 mL with the same solvent. To 1.0 mL of the solution, add 12 mL of *dimethyl sulfoxide R* and dilute to 50.0 mL with *water R*. To 1.0 mL of this solution, add 12 mL of *dimethyl sulfoxide R* and dilute to 50.0 mL with *water R*.

Injection 50 µL.

Identification of impurities Use the chromatogram obtained with the reference solution to identify the peak due to impurity B.

Retention time Impurity B = about 7 min.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (2 ppm).

Loss on drying (2.2.32)

Maximum 0.25 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 32.34 mg of $C_{15}H_{21}N_3O_3S$.

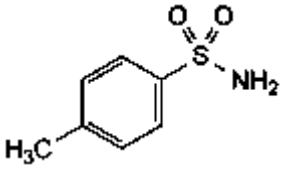
IMPURITIES

Specified impurities *B, F.*

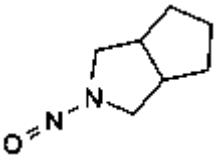
www.webofpharma.com

https://thuocngocanh.com/

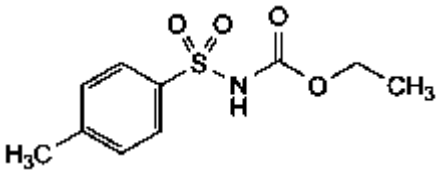
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, G.*



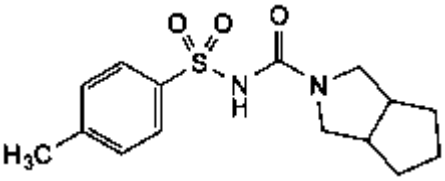
A. 4-methylbenzene-1-sulfonamide,



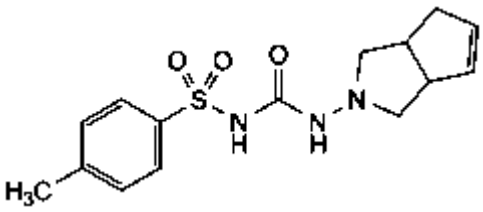
B. 2-nitrosooctahydrocyclopenta[*c*]pyrrole,



C. ethyl (4-methylbenzene-1-sulfonyl)carbamate,



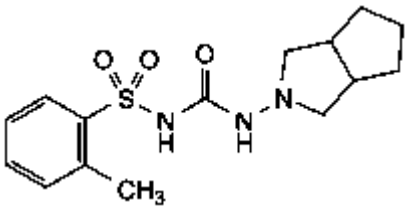
D. *N*-(4-methylbenzene-1-sulfonyl)hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-carboxamide,



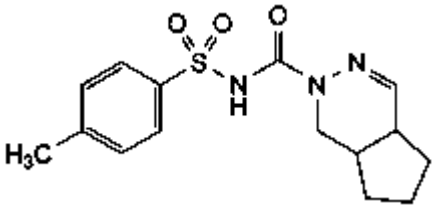
E. 4-methyl-*N*-[(3,3a,4,6a-tetrahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)carbamoyl]benzene-sulfonamide,

www.webofpharma.com

https://thuvienthuocngocanh.com/



F. 2-methyl-*N*-[(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)carbamoyl]benzene-1-sulfonamide,



G. *N*-[(4-methylbenzene-1-sulfonyl)-1,4a,5,6,7,7a-hexahydro-2*H*-cyclopenta[*d*]pyridazine-2-carboxamide.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gliclazide Tablets

General Notices

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

DEFINITION

Gliclazide Tablets contain Gliclazide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of gliclazide, $C_{15}H_{21}N_3O_3S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.16 g of Gliclazide with 20 mL of *dichloromethane*, centrifuge and evaporate the supernatant liquid to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of gliclazide *(RS 168)*.

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 900 mL of *phosphate buffer pH 7.4*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a 10-mL sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, expected to contain 0.00125% w/v of Gliclazide at 226 nm and 290 nm, Appendix II B using *phosphate buffer pH 7.4* in the reference cell. Correct the absorbance obtained at 226 nm by subtracting the absorbance obtained at 290 nm.

(2) Measure the *absorbance* of a 0.00124% w/v solution of *gliclazide BPCRS* using *phosphate buffer pH 7.4* in the reference cell. Correct the absorbance obtained at 226 nm by subtracting the absorbance obtained at 290 nm.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of $C_{15}H_{21}N_3O_3S$ in the medium from the absorbances obtained and using the declared content of $C_{15}H_{21}N_3O_3S$ in *gliclazide BPCRS*.

LIMITS

The amount of gliclazide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use.

Solution A: 45 volumes of *acetonitrile* and 55 volumes of *water*.

(1) Shake a quantity of the powdered tablets containing 0.8 g of Gliclazide with 160 mL of *acetonitrile* and dilute to 200 mL with *acetonitrile*. Filter and dilute 1 volume of the filtrate to 5 volumes with a mixture of 1 volume of *acetonitrile* and 2 volumes of *water*.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A. Further dilute 1 volume to 5 volumes with solution A.
(3) Dissolve 5 mg of *gliclazide BPCRS* and 15 mg of *gliclazide impurity F BPCRS* in 25 mL of *acetonitrile*, dilute to 50 mL with *water* and dilute 1 volume of the resulting solution to 20 volumes with solution A.
(4) Dissolve 8 mg of *gliclazide impurity F BPCRS* in 25 mL of *acetonitrile*, dilute to 50 mL with *water* and dilute 1 volume of the resulting solution to 100 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *octylsilyl silica gel for chromatography* (4 µm) (Superspher 60 RP-8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.9 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 235 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

0.1 volumes of *triethylamine*, 0.1 volumes of *trifluoroacetic acid*, 45 volumes of *acetonitrile* and 55 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to gliclazide (retention time about 16 minutes) is: impurity F, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gliclazide and impurity F is at least 1.8.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal in the chromatogram obtained with solution (2) (0.2%).

The total impurity content is not greater than 0.4%.

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing 0.8 g of Gliclazide with 160 mL of *acetonitrile* and dilute to 200 mL with *acetonitrile*. Filter and dilute 1 volume of the filtrate to 20 volumes with a mixture of 2 volumes of *acetonitrile* and 3 volumes of *water*.
(2) Dissolve 40 mg of *gliclazide BPCRS* in 10 mL of *acetonitrile* and dilute to 200 mL with a mixture of 2 volumes of *acetonitrile* and 3 volumes of *water*.
(3) Dissolve 5 mg of *gliclazide BPCRS* and 15 mg of *gliclazide impurity F BPCRS* in 25 mL of *acetonitrile*, dilute to 50 mL with *water* and dilute 1 volume of the resulting solution to 20 volumes with a mixture of 45 volumes of *acetonitrile* and 55 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to gliclazide and impurity F is at least 1.8.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{21}N_3O_3S$ in the tablets using the declared content of $C_{15}H_{21}N_3O_3S$ in *gliclazide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C, D, E, F and G listed under Gliclazide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

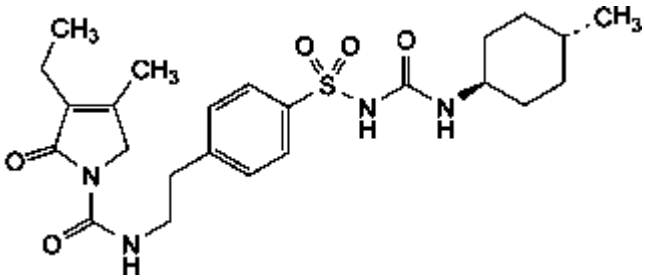
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glimepiride

General Notices

(Ph. Eur. monograph 2223)



$C_{24}H_{34}N_4O_5S$ 490.6 *93479-97-1*

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

Preparation

Glimepiride Tablets

Ph Eur

DEFINITION

1-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-*trans*-(4-methylcyclohexyl)urea.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in dimethylformamide, slightly soluble in methylene chloride, very slightly soluble in methanol.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *glimepiride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *dimethylformamide R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29). *Store the solutions at a temperature not exceeding 12 °C and for not more than 15 h.*

Solvent mixture *water for chromatography R*, *acetonitrile for chromatography R* (1:4 *V/V*).

Test solution Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *glimepiride for system suitability CRS* (containing impurities B, C and D) in 2.0 mL of the test solution.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 20.0 mg of *glimepiride CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase Dissolve 0.5 g of *sodium dihydrogen phosphate R* in 500 mL of *water for chromatography R* and adjust to pH 2.5 with *phosphoric acid R*. Add 500 mL of *acetonitrile for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 228 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time 2.5 times the retention time of glimepiride.

Relative retention With reference to glimepiride (retention time = about 17 min): impurity B = about 0.2; impurity C = about 0.3; impurity D = about 1.1.

System suitability Reference solution (a):

www.webofpharma.com

https://thuocngocanh.com/

— *resolution*: minimum 4.0 between the peaks due to impurities B and C.

Limits:

— *impurity B*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent),

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent),

— *sum of impurities other than B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Impurity A

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 10.0 mg of the substance to be examined in 5 mL of *methylene chloride R* and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 0.8 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.0 mg of *glimepiride for impurity A identification CRS* in 1 mL of *methylene chloride R* and dilute to 4.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3 mm;

— *stationary phase*: *diol silica gel for chromatography R* (5 µm).

Mobile phase *anhydrous acetic acid R*, *2-propanol R*, *heptane R* (1:100:899 *V/V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 228 nm.

Injection 10 µL.

Run time 1.5 times the retention time of glimepiride.

Identification of impurities Use the chromatogram supplied with *glimepiride for impurity A identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to glimepiride (retention time = about 14 min): impurity A = about 0.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to glimepiride.

Limit:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent).

Water (2.5.32)

Maximum 0.5 per cent.

Dissolve 0.250 g in *dimethylformamide R* and dilute to 5.0 mL with the same solvent. Carry out the test on 1.0 mL of solution. Carry out a blank test.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

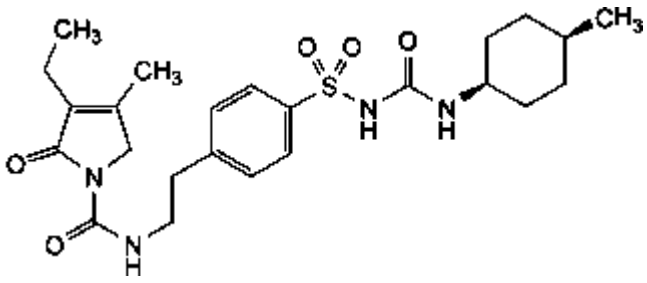
Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{24}H_{34}N_4O_5S$ from the areas of the peaks and the assigned content of *glimepiride CRS*.

IMPURITIES

Specified impurities *A, B, D.*

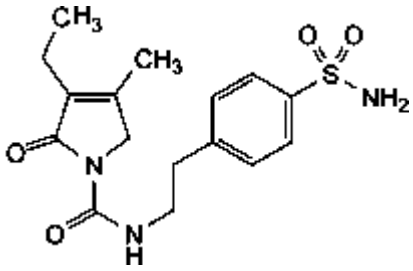
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *C, E, F, G, H, I, J.*



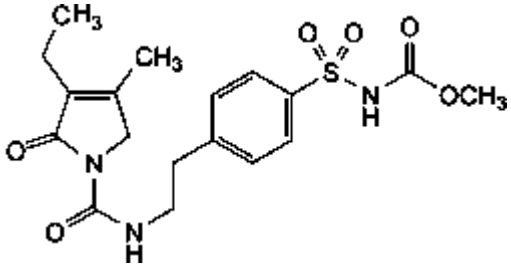
A. 1-[[4-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]-3-(*cis*-4-methylcyclohexyl)urea,

www.webofpharma.com

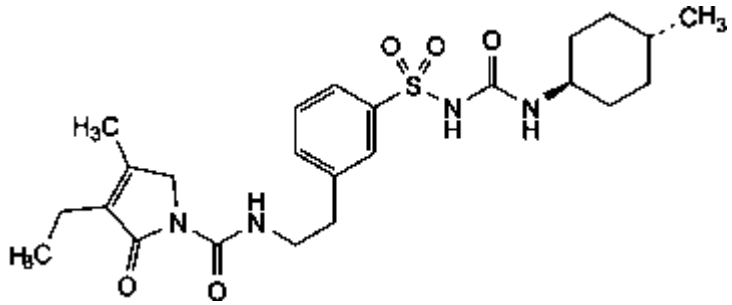
https://thuvienthuocngocanh.com/



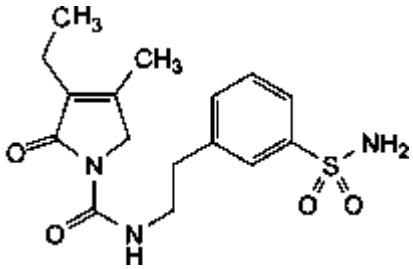
B. 3-ethyl-4-methyl-2-oxo-*N*-[2-(4-sulfamoylphenyl)ethyl]-2,3-dihydro-1*H*-pyrrole-1-carboxamide,



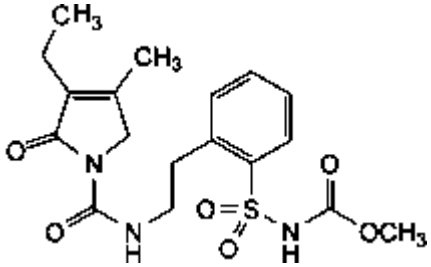
C. methyl [[4-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]carbamate,



D. 1-[[3-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea,



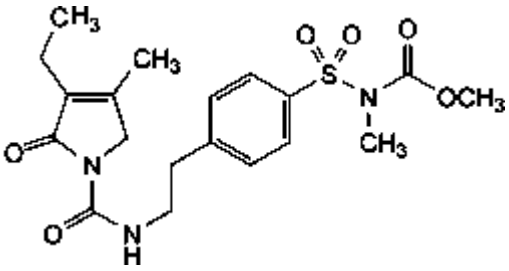
E. 3-ethyl-4-methyl-2-oxo-*N*-[2-(3-sulfamoylphenyl)ethyl]-2,3-dihydro-1*H*-pyrrole-1-carboxamide,



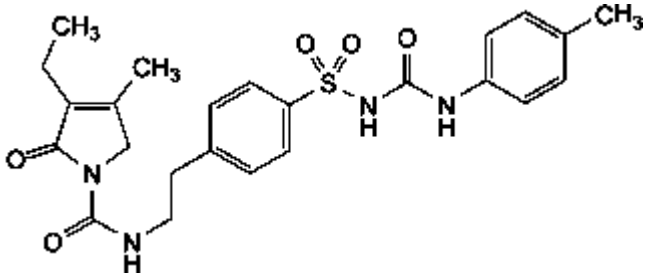
F. methyl [[2-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]carbamate,

www.webofpharma.com

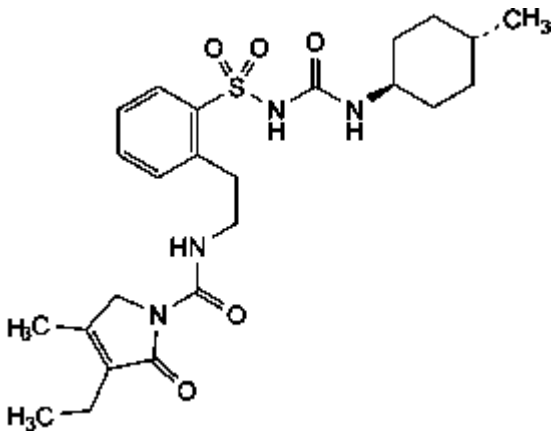
https://thuocngocanh.com/



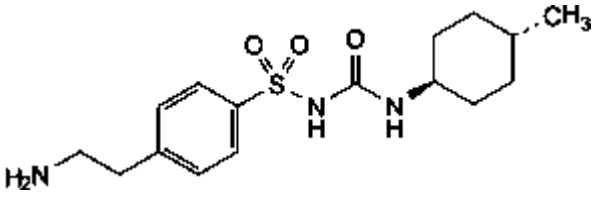
G. methyl [[4-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]methylcarbamate,



H. 1-[[4-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]-3-(4-methylphenyl)urea,



I. 1-[[2-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea,



J. 1-[[4-(2-aminoethyl)phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glimepiride Tablets

General Notices

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

DEFINITION

Glimepiride Tablets contain Glimepiride.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of glimepiride, $C_{24}H_{34}N_4O_5S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Extract a quantity of the powdered tablets containing 10 mg of Glimepiride with 20 mL of *acetonitrile*, centrifuge and filter the supernatant liquid, evaporate to dryness at a temperature not exceeding 30°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of glimepiride (*RS 463*).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of a pH 7.8 buffer solution prepared by mixing 14.5 g of *potassium dihydrogen phosphate* and 277.76 g of *sodium dihydrogen orthophosphate* with sufficient water to make 25 litres, adjusted to pH 7.8 with 10% v/v *orthophosphoric acid* or 1M *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Store the solutions at a temperature not exceeding 12° and use within 15 hours*.

www.webofpharma.com

https://thuocngocanh.com/

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtrate, diluted with the dissolution medium, if necessary, to produce a solution expected to contain 0.0001% w/v of Glimepiride.

(2) Dilute 1 volume of a 0.001% w/v solution of *glimepiride BPCRS* in *acetonitrile* to 10 volumes with the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Lichrospher RP 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use an auto-sampler temperature of 12°.

(f) Use a detection wavelength of 228 nm.

(g) Inject 50 µL of each solution.

MOBILE PHASE

Equal volumes of a 0.1% w/v solution of *sodium dihydrogen phosphate dihydrate* and *acetonitrile R1*, the pH adjusted to 2.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the retention time of glimepiride is about 8 minutes.

DETERMINATION OF CONTENT

Calculate the total content of glimepiride, $C_{24}H_{34}N_4O_5S$, in the medium from the chromatograms obtained and using the declared content of $C_{24}H_{34}N_4O_5S$ in *glimepiride BPCRS*.

LIMITS

The amount of glimepiride released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *water* and 4 volumes of *acetonitrile*. *Store the solutions at a temperature not exceeding 12° and use within 15 hours*.

(1) Shake a quantity of the powdered tablets containing 2 mg of Glimepiride with 8 mL of a mixture of 1 volume of *water* and 4 volumes of *acetonitrile*. Dilute to 10 mL with the same solvent, centrifuge and use the supernatant liquid.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.04% w/v of *glimepiride for system suitability BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (4 µm) (Supelco Superspher RP 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

www.webofpharma.com

https://thuocngocanh.com/

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use an auto-sampler temperature of 12°.

(f) Use a detection wavelength of 228 nm.

(g) Inject 10 µL of each solution.

(h) Allow the chromatography to proceed for 3.5 times the retention time of the peak due to glimepiride.

MOBILE PHASE

Equal volumes of a 0.1% w/v solution of *sodium dihydrogen phosphate dihydrate* and *acetonitrile R1*, the pH adjusted to 2.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to glimepiride (retention time about 17 minutes) are: impurity B, about 0.24 and impurity C, about 0.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and impurity C is at least 4.0.

LIMITS

Identify the peak due to impurity B in solution (1) using solution (3) and multiply the peak area by the correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the peak due to glimepiride in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or 2% w/w of Glimepiride comply with the requirements stated under Tablets using the following method of analysis.

Carry out the method for liquid chromatography, Appendix III D, using the following solutions. *Store the solutions at a temperature not exceeding 12° and use within 15 hours*.

(1) To one tablet add 1 mL of *water* and allow to disintegrate. Add 8 mL of a solution containing 1 volume of *water* and 9 volumes of *acetonitrile*, mix with the aid of ultrasound for 15 minutes. Dilute to 10 mL with the same solvent, centrifuge and use the supernatant liquid, diluted if necessary with mobile phase to produce a solution expected to contain 0.01% w/v of Glimepiride.

www.webofpharma.com

https://thuocngocanh.com/

(2) 0.01% w/v of *glimepiride BPCRS* in a mixture of 1 volume of *water* and 4 volumes of *acetonitrile*.

(3) 0.04% w/v of *glimepiride for system suitability BPCRS* in a mixture of 1 volume of *water* and 4 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Lichrospher RP 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use an auto-sampler temperature of 12°.

(f) Use a detection wavelength of 228 nm.

(g) Inject 10 µL of each solution.

MOBILE PHASE

Equal volumes of a 0.1% w/v solution of *sodium dihydrogen phosphate dihydrate* and *acetonitrile R1*, the pH adjusted to 2.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and impurity C is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{34}N_4O_5S$ in each tablet using the declared content of $C_{24}H_{34}N_4O_5S$ in *glimepiride BPCRS*.

ASSAY

For tablets containing less than 2 mg, or 2% w/w of glimepiride

Use the average of the individual results determined in the test for Uniformity of content.

For tablets containing 2 mg or more, or 2% w/w or more of glimepiride

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions

(1) To a quantity of powdered tablets containing 10 mg of Glimepiride, add 80 mL of a solution containing 1 volume of *water* and 9 volumes of *acetonitrile*, mix with the aid of ultrasound. Add sufficient of a mixture containing 1 volume of *water* and 9 volumes of *acetonitrile* to produce 100 mL, centrifuge and use the supernatant liquid.

(2) 0.01% w/v of *glimepiride BPCRS* in a mixture of 1 volume of *water* and 4 volumes of *acetonitrile*.

(3) 0.04% w/v of *glimepiride for system suitability BPCRS* in a mixture of 1 volume of *water* and 4 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and impurity C is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{34}N_4O_5S$ in the tablets using the declared content of $C_{24}H_{34}N_4O_5S$ in *glimepiride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Glimepiride.

© Crown Copyright 2022

www.webofpharma.com

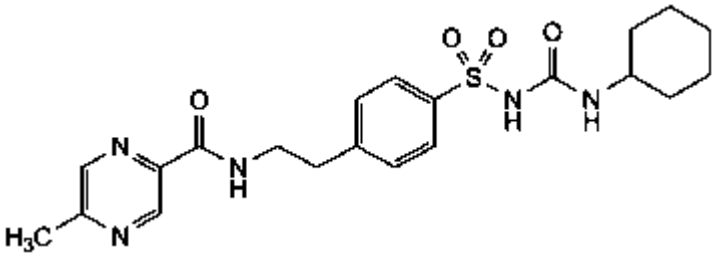
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glipizide

General Notices

(Ph. Eur. monograph 0906)



$C_{21}H_{27}N_5O_4S$ 445.5 *29094-61-9*

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

Preparation

Glipizide Tablets

Ph Eur

DEFINITION

N-[2-[4-[(Cyclohexylcarbamoyl)sulfamoyl]phenyl]ethyl]-5-methylpyrazine-2-carboxamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very slightly soluble in acetone and in methylene chloride, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *glipizide CRS*.

B. Melting point (2.2.14).

Determination A Determine the melting point of the substance to be examined.

Result A 203 °C to 208 °C.

Determination B Mix equal parts of the substance to be examined and *glipizide CRS* and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mix 40 volumes of *acetonitrile R* and 60 volumes of *water R* previously adjusted to pH 3.5 with *acetic acid R*.

Test solution Dissolve 20.0 mg of the substance to be examined in 20.0 mL of *methanol R* using sonication and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 6.0 mg of *glipizide impurity A CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *glipizide impurity C CRS* in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 100 mL with the solvent mixture.

Reference solution (d) Dissolve 2 mg of *glipizide impurity D CRS* in the solvent mixture and dilute to 250 mL with the solvent mixture. Dilute 1 mL of the solution to 20 mL with reference solution (b).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

www.webofpharma.com

https://thuocngocanh.com/

— *mobile phase A*: *water for chromatography R* adjusted to pH 3.5 with *acetic acid R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	75	25
5 - 12	75 → 65	25 → 35
12 - 20	65	35
20 - 25	65 → 50	35 → 50
25 - 30	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity D.

Relative retention With reference to glipizide (retention time = about 22 min): impurity A = about 0.25; impurity D = about 0.27; impurity C = about 1.2.

System suitability Reference solution (d):

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.7;

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: maximum 0.5 per cent;

www.webofpharma.com

https://nhathuocngocanh.com/

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurity B

Gas chromatography (2.2.28).

Internal standard solution Dissolve 25.0 mg of *decane R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *methylene chloride R*.

Test solution (a) Dissolve 1.000 g of the substance to be examined in 50 mL of a 12 g/L solution of *sodium hydroxide R* and shake with 2 quantities, each of 5.0 mL, of *methylene chloride R*. Use the combined lower layers.

Test solution (b) Dissolve 1.000 g of the substance to be examined in 50 mL of a 12 g/L solution of *sodium hydroxide R* and shake with 2 quantities, each of 5.0 mL, of the internal standard solution. Use the combined lower layers.

Reference solution Dissolve 10.0 mg of *cyclohexylamine R* (impurity B) in a 17.5 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. To 1.0 mL of this solution add 50 mL of a 12 g/L solution of *sodium hydroxide R* and shake with 2 quantities, each of 5.0 mL, of the internal standard solution. Use the combined lower layers.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.8 mL/min.

Split ratio 1:11.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 4	40
	4 - 20	40 → 200
	20 - 25	200
Injection port		250
Detector		270

Detection Flame ionisation.

www.webofpharma.com

https://thuocngocanh.com/

Injection 1 µL.

Elution order Impurity B, decane.

System suitability:

— *resolution*: minimum 7 between the peaks due to impurity B and the internal standard in the chromatogram obtained with the reference solution;

— there is no peak with the same retention time as that of the internal standard in the chromatogram obtained with test solution (a).

Calculate the ratio (*R*) of the area of the peak due to impurity B to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with test solution (b), calculate the ratio of the area of any peak due to impurity B to the area of the peak due to the internal standard.

Limit:

— *impurity B*: not more than *R* (100 ppm).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g in 50 mL of *dimethylformamide R*. Add 0.2 mL of *quinaldine red solution R*. Titrate with *0.1 M lithium methoxide* until the colour changes from red to colourless.

1 mL of *0.1 M lithium methoxide* is equivalent to 44.55 mg of $C_{21}H_{27}N_5O_4S$.

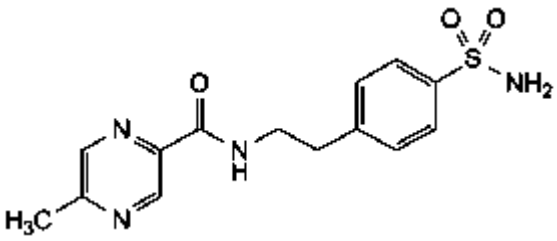
IMPURITIES

Specified impurities *A, B, C.*

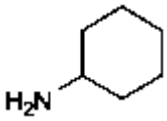
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, E, F, G, H, I, J.*

www.webofpharma.com

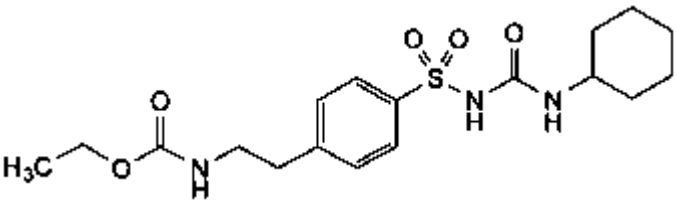
https://thuocngocanh.com/



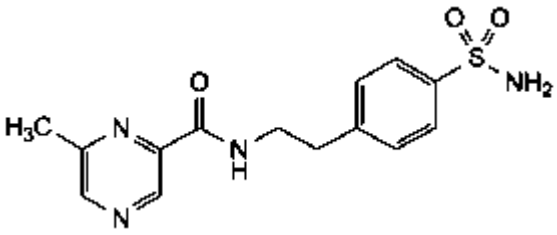
A. 5-methyl-*N*-[2-(4-sulfamoylphenyl)ethyl]pyrazine-2-carboxamide,



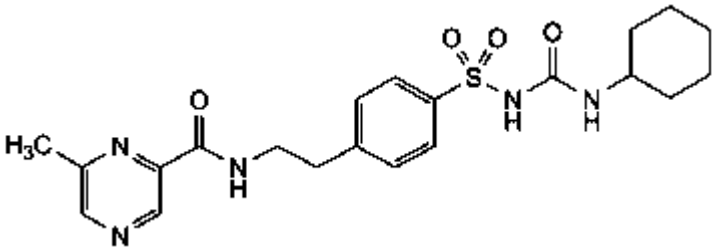
B. cyclohexanamine (cyclohexylamine),



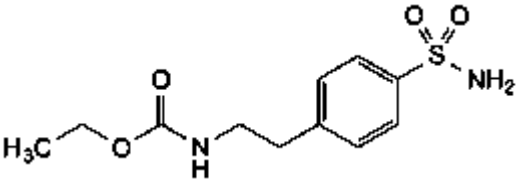
C. ethyl [2-[4-[(cyclohexylcarbamoyl)sulfamoyl]phenyl]ethyl]carbamate,



D. 6-methyl-*N*-[2-(4-sulfamoylphenyl)ethyl]pyrazine-2-carboxamide,



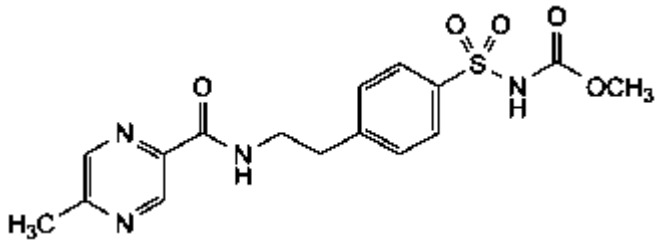
E. *N*-[2-[4-[(cyclohexylcarbamoyl)sulfamoyl]phenyl]ethyl]-6-methylpyrazine-2-carboxamide,



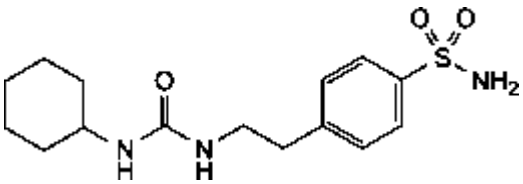
F. ethyl [2-(4-sulfamoylphenyl)ethyl]carbamate,

www.webofpharma.com

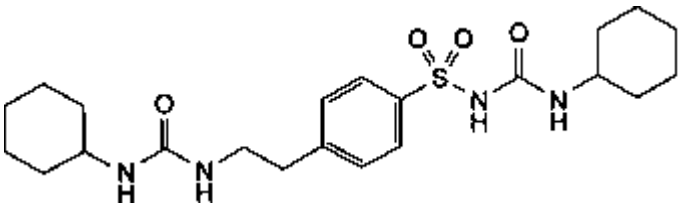
https://thuocngocanh.com/



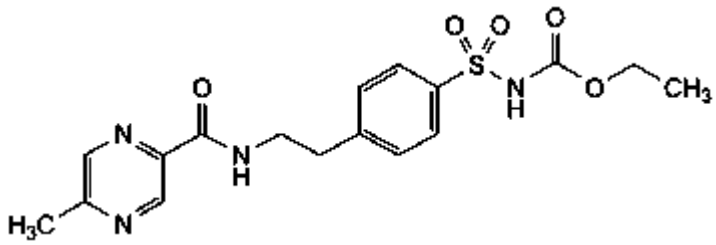
G. methyl [4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzene-1-sulfonyl]carbamate,



H. 4-[2-[(cyclohexylcarbamoyl)amino]ethyl]benzene-1-sulfonamide,



I. *N*-(cyclohexylcarbamoyl)-4-[2-[(cyclohexylcarbamoyl)amino]ethyl]benzene-1-sulfonamide,



J. ethyl [4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzene-1-sulfonyl]carbamate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glipizide Tablets

General Notices

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

DEFINITION

Glipizide Tablets contain Glipizide.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of glipizide $C_{21}H_{27}N_5O_4S$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 320 nm of the final solution obtained in the Assay exhibits maxima at 226 nm and 274 nm.

B. Shake a quantity of the powdered tablets containing 25 mg of Glipizide with 10 mL of *dichloromethane* for 5 minutes, filter, dry the filtrate with *anhydrous sodium sulfate*, filter again and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of glipizide *(RS 169)*.

TESTS

Related substances

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing 0.1 g of Glipizide with four 10-mL quantities of *acetone*, evaporate the combined extracts to dryness under reduced pressure at a temperature not exceeding 30° and dissolve the residue in sufficient of a mixture of equal volumes of *dichloromethane* and *methanol* to produce 5 mL.

(2) Dilute 1 volume of solution (1) to 200 volumes with a mixture of equal volumes of *dichloromethane* and *methanol*.

(3) Dilute 1 volume of solution (1) to 500 volumes with the same solvent mixture.

(4) 0.010% w/v of *glipizide impurity A EPCRS* (5-methyl-*N*-[2-(4-sulfamoylphenyl)ethyl]pyrazine-2-carboxamide) in a mixture of equal volumes of *dichloromethane* and *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).

www.webofpharma.com

https://thuocngocanh.com/

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

20 volumes of *ethyl acetate*, 20 volumes of *anhydrous formic acid* and 40 volumes of *dichloromethane*.

LIMITS

In the chromatogram obtained with solution (1);

any spot corresponding to glipizide impurity A is not more intense than the spot in the chromatogram obtained with solution (4) (0.5%);

any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (2) (0.5%);

and not more than two such spots are more intense than the spot in the chromatogram obtained with solution (3) (0.2%).

ASSAY

Weigh and powder 20 tablets. To a quantity of the powder containing 15 mg of Glipizide add 30 mL of *methanol*, heat gently on a water bath whilst shaking, cool and add sufficient *methanol* to produce 50 mL. Filter and dilute 5 mL of the filtrate to 50 mL with *methanol*. Measure the *absorbance* of the resulting solution at the maximum at 274 nm, Appendix II B, using *methanol* in the reference cell. Calculate the content of $C_{21}H_{27}N_5O_4S$ taking 237 as the value of A(1%, 1 cm) at the maximum at 274 nm.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

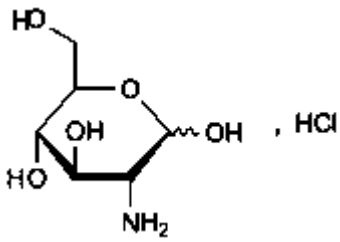
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glucosamine Hydrochloride

General Notices

(Ph. Eur. monograph 2446)



$C_6H_{14}ClNO_5$ 215.6 *66-84-2*

Ph Eur

DEFINITION

2-Amino-2-deoxy-D-glucopyranose hydrochloride.

Isolated from natural sources or produced by fermentation.

Content

98.0 per cent to 102.0 per cent (dried substance).

PRODUCTION

The animals from which glucosamine hydrochloride is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in methanol, practically insoluble in acetone.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *glucosamine hydrochloride CRS*.

B. 1 mL of solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

C. Specific optical rotation (see Tests).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dilute 5.0 mL of solution S to 25.0 mL with *water R*.

pH (2.2.3)

3.0 to 5.0 for solution S.

Specific optical rotation (2.2.7)

+ 70.0 to + 74.0 (dried substance), determined on solution S.

Examine 3 h after preparation of solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution To 0.300 g of the substance to be examined add 80 mL of the mobile phase and sonicate for 10 min. Cool to room temperature and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *2-methylpyrazine CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *glucosamine for system suitability CRS* (containing impurities B and C) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 30 °C.

www.webofpharma.com

https://thuocngocanh.com/

Mobile phase Dissolve 0.5 g of *sodium heptanesulfonate R* in *water for chromatography R*, add 0.5 mL of *phosphoric acid R* and 4 mL of a 56 g/L solution of *potassium hydroxide R* and dilute to 1000 mL with *water for chromatography R*; to 1000 mL of this solution add 50 mL of *acetonitrile R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 195 nm.

Injection 20 µL.

Run time Twice the retention time of 2-methylpyrazine.

Retention time 2-methylpyrazine = about 9 min.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and C.

Limits:

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

ASSAY

Dissolve 0.200 g in 50 mL of *water R* and add 1.0 mL of *0.1 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

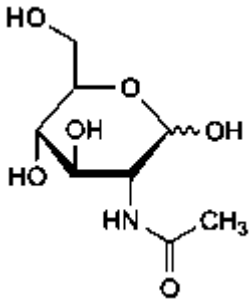
1 mL of *0.1 M sodium hydroxide* is equivalent to 21.56 mg of $C_6H_{14}ClNO_5$.

www.webofpharma.com

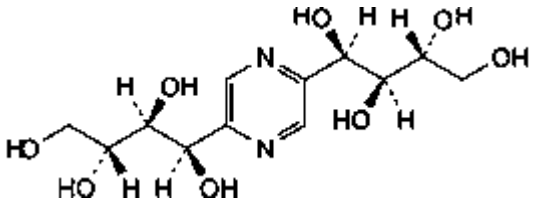
https://thuocngocanh.com/

IMPURITIES

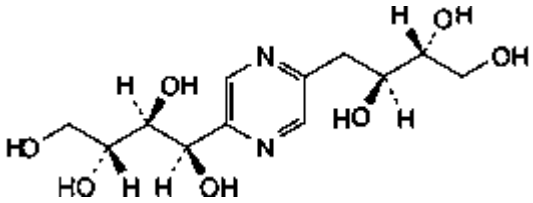
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E.*



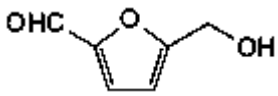
A. 2-(acetylamino)-2-deoxy-D-glucopyranose (*N*-acetylglucosamine),



B. (1*R*,1′*R*,2*S*,2′*S*,3*R*,3′*R*)-1,1′-pyrazine-2,5-diylbis(butane-1,2,3,4-tetrol) (fructosazine),



C. (1*R*,2*S*,3*R*)-1-[5-[(2*S*,3*R*)-2,3,4-trihydroxybutyl]pyrazin-2-yl]butane-1,2,3,4-tetrol (deoxyfructosazine),



E. 5-(hydroxymethyl)furan-2-carbaldehyde (5-hydroxymethylfurfural).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

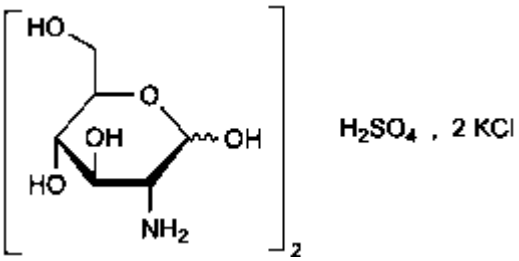
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glucosamine Sulfate Potassium Chloride

General Notices

(Ph. Eur. monograph 2708)



$C_{12}H_{28}Cl_2K_2N_2O_{14}S$ 606 *216699-44-4*

Ph Eur

DEFINITION

Bis(2-amino-2-deoxy-D-glucopyranose) sulfate bis(potassium chloride).

Substance prepared from glucosamine hydrochloride isolated from natural sources or produced by fermentation, and potassium sulfate.

Content

98.0 per cent to 102.0 per cent (dried substance).

PRODUCTION

The animals from which glucosamine sulfate potassium chloride is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in methanol, practically insoluble in acetone.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *glucosamine sulfate potassium chloride CRS*.

C. It gives reaction (a) of chlorides (2.3.1).

D. It gives reaction (a) of sulfates (2.3.1).

E. 1 mL of solution S (see Tests) gives reaction (a) of potassium (2.3.1).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dilute 5.0 mL of solution S to 25.0 mL with *water R*.

pH (2.2.3)

3.0 to 5.0 for solution S.

Specific optical rotation (2.2.7)

+ 47.0 to + 53.0 (dried substance), determined on solution S.

Examine 3 h after preparation of solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution To 0.42 g of the substance to be examined add 80 mL of the mobile phase and sonicate for 10 min. Cool to room temperature and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *2-methylpyrazine CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *glucosamine for system suitability CRS* (containing impurities B and C) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm) (3 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 30 °C.

Mobile phase Dissolve 0.5 g of *sodium heptanesulfonate R* in *water for chromatography R*, add 0.5 mL of *phosphoric acid R*, 4 mL of a 56 g/L solution of *potassium hydroxide R* and dilute to 1000 mL with *water for chromatography R*, then add 50 mL of *acetonitrile R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 195 nm.

Injection 20 µL.

Run time Twice the retention time of 2-methylpyrazine.

Retention time 2-methylpyrazine = about 9 min.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and C.

Calculation of percentage contents:

— for each impurity, use the concentration of 2-methylpyrazine in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

27.0 per cent to 31.0 per cent, determined on 1.0 g.

Ignite first at 600 ± 50 °C for 2 h. Do not repeat the moistening with *sulfuric acid R* between any re-ignition.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

ASSAY

www.webofpharma.com

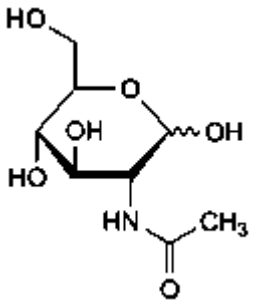
https://thuocngocanh.com/

Dissolve 0.280 g in 50 mL of *water R* and add 1.0 mL of *0.1 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

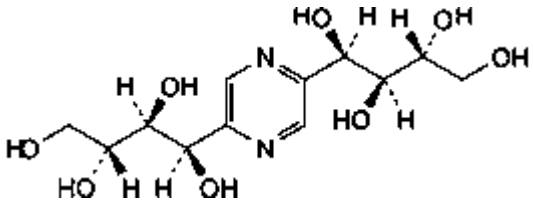
1 mL of *0.1 M sodium hydroxide* is equivalent to 30.28 mg of $C_{12}H_{28}Cl_2K_2N_2O_{14}S$.

IMPURITIES

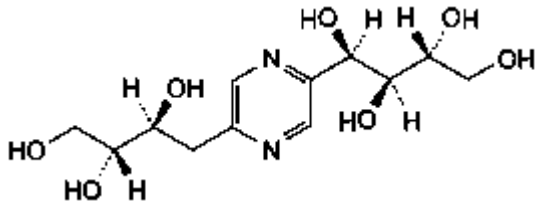
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E.*



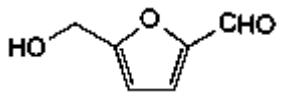
A. 2-(acetylamino)-2-deoxy-D-glucopyranose (*N*-acetylglucosamine),



B. (1*R*,1′*R*,2*S*,2′*S*,3*R*,3′*R*)-1,1′-pyrazine-2,5-diylbis (butane-1,2,3,4-tetrol) (fructosazine),



C. (1*R*,2*S*,3*R*)-1-[5-[(2*S*,3*R*)-2,3,4-trihydroxybutyl]pyrazin-2-yl]butane-1,2,3,4-tetrol (deoxyfructosazine),



E. 5-(hydroxymethyl)furan-2-carbaldehyde (5-hydroxymethylfurfural).

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

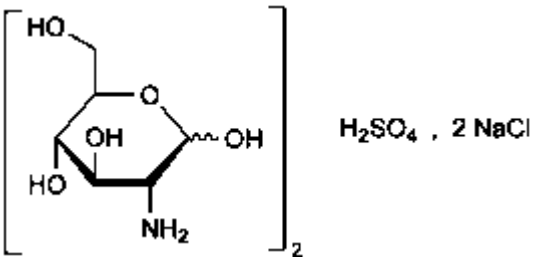
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glucosamine Sulfate Sodium Chloride

General Notices

(Ph. Eur. monograph 2447)



$C_{12}H_{28}Cl_2N_2Na_2O_{14}S$ 573.3 *216447-62-0*

Ph Eur

DEFINITION

Bis(2-amino-2-deoxy-D-glucopyranose) sulfate bis(sodium chloride).

Substance prepared from glucosamine hydrochloride isolated from natural sources or produced by fermentation, and sodium sulfate.

Content

98.0 per cent to 102.0 per cent (dried substance).

PRODUCTION

The animals from which glucosamine sulfate sodium chloride is derived must fulfil the requirements for the health of animals suitable for human consumption.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, sparingly soluble in methanol, practically insoluble in acetone.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *glucosamine sulfate sodium chloride CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

C. 1 mL of solution S (see Tests) gives reaction (a) of sodium (*2.3.1*).

D. It gives reaction (a) of sulfates (*2.3.1*).

E. Specific optical rotation (see Tests).

TESTS

Solution S

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution

The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dilute 5.0 mL of solution S to 25.0 mL with *water R*.

pH (*2.2.3*)

3.0 to 5.0 for solution S.

Specific optical rotation (*2.2.7*)

+ 50.0 to + 55.0 (dried substance), determined on solution S.

Examine 3 h after preparation of solution S.

Related substances

Liquid chromatography (*2.2.29*).

Test solution To 0.40 g of the substance to be examined add 80 mL of the mobile phase and sonicate for 10 min. Cool to room temperature and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 25.0 mg of *2-methylpyrazine CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *glucosamine for system suitability CRS* (containing impurities B and C) in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

www.webofpharma.com

https://thuocngocanh.com/

— *temperature*: 30 °C.

Mobile phase Dissolve 0.5 g of *sodium heptanesulfonate R* in *water for chromatography R*, add 0.5 mL of *phosphoric acid R* and 4 mL of a 56 g/L solution of *potassium hydroxide R* and dilute to 1000 mL with *water for chromatography R*; to 1000 mL of this solution add 50 mL of *acetonitrile R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 195 nm.

Injection 20 µL.

Run time Twice the retention time of 2-methylpyrazine.

Retention time 2-methylpyrazine = about 9 min.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities B and C.

Limits:

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*)

23.5 per cent to 26.0 per cent, determined on 1.0 g.

Ignite first at 600 ± 50 °C for 2 h. Do not repeat the moistening with *sulfuric acid R* between any re-ignition.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

ASSAY

www.webofpharma.com

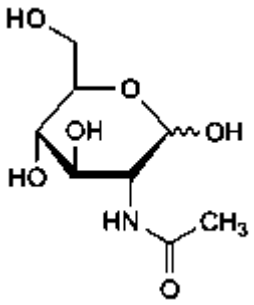
https://thietbiuocngocanh.com/

Dissolve 0.250 g in 50 mL of *water R* and add 1.0 mL of *0.1 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

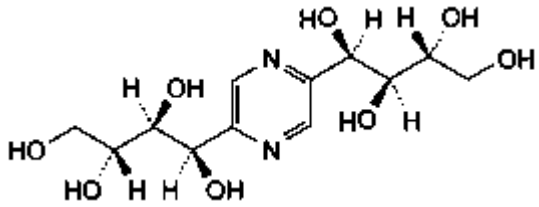
1 mL of *0.1 M sodium hydroxide* is equivalent to 28.67 mg of $C_{12}H_{28}Cl_2N_2Na_2O_{14}S$.

IMPURITIES

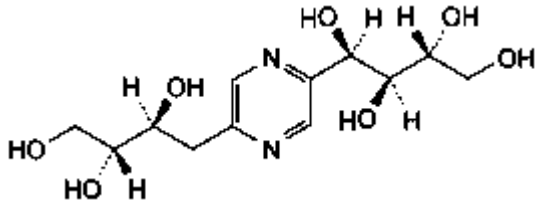
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E.*



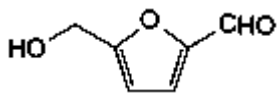
A. 2-(acetylamino)-2-deoxy-D-glucopyranose (*N*-acetylglucosamine),



B. (1*R*,1′*R*,2*S*,2′*S*,3*R*,3′*R*)-1,1′-pyrazine-2,5-diylbis (butane-1,2,3,4-tetrol) (fructosazine),



C. (1*R*,2*S*,3*R*)-1-[5-[(2*S*,3*R*)-2,3,4-trihydroxybutyl] pyrazin-2-yl]butane-1,2,3,4-tetrol (deoxyfructosazine),



E. 5-(hydroxymethyl)furan-2-carbaldehyde (5-hydroxymethylfurfural).

Ph Eur

www.webofpharma.com

https://thuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

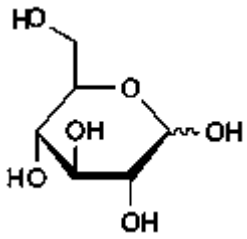
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Glucose[1]

General Notices

Anhydrous Glucose

(Ph. Eur. monograph 0177)



$C_6H_{12}O_6$ 180.2 *50-99-7*

Preparations

Glucose Infusion

Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution

Oral Rehydration Salts

Potassium Chloride and Glucose Intravenous Infusion

Potassium Chloride, Sodium Chloride and Glucose Intravenous Infusion

Sodium Chloride and Glucose Intravenous Infusion

Ph Eur

DEFINITION

D-Glucopyranose.

It is derived from starch.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

www.webofpharma.com

https://thuocngocanh.com/

♦ CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).♦

IDENTIFICATION

First identification: ◊ A◊ , B, E.

◊ *Second identification: C, D.*◊

◊ A. Specific optical rotation (2.2.7): + 52.5 to + 53.3 (anhydrous substance).
Dissolve 10.0 g in 80 mL of *water R*, add 0.2 mL of *dilute ammonia R1*, allow to stand for 30 min and dilute to 100.0 mL with *water R*.◊

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

◊ C. Thin-layer chromatography (2.2.27).

Solvent mixture *water R*, *methanol R* (40:60 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution Dissolve 10 mg of *glucose monohydrate CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *methanol R*, *anhydrous acetic acid R*, *methylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately since a slight excess of water produces cloudiness.

Application 2 µL; thoroughly dry the points of application.

Development A Over 3/4 of the plate.

Drying A In a current of warm air.

Development B Immediately, over 3/4 of the plate, after renewing the mobile phase.

Drying B In a current of warm air.

Detection Treat with a solution of 0.5 g of *thymol R* in a mixture of 5 mL of *sulfuric acid R* and 95 mL of *ethanol (96 per cent) R*; heat at 130 °C for 10 min.

www.webofpharma.com

https://thuocngocanh.com/

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 5 g in *water R* and dilute to 10 mL with the same solvent. To 0.5 mL of the solution, add 0.2 g of *resorcinol R* and 9 mL of *dilute hydrochloric acid R* and heat on a water-bath for 2 min. No red colour develops.◊

E. Water (see Tests).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 10.0 g in *water R*, heating on a water-bath.

Conductivity (*2.2.38*)

Maximum 20 $\mu S \cdot cm^{-1}$.

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.300 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.330 g of *glucose monohydrate CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 250.0 mL with *water R*.

Reference solution (c) Dilute 25.0 mL of reference solution (b) to 200.0 mL with *water R*.

Reference solution (d) Dissolve 5 mg of *fructose R* (impurity D), 5 mg of *maltose monohydrate R* (impurity A) and 5 mg of *maltotriose R* (impurity C) in *water R* and dilute to 50 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 85 ± 1 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.3 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Refractometer maintained at a constant temperature (40 °C for example).

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 1.5 times the retention time of glucose.

Relative retention With reference to glucose (retention time = about 21 min): impurity C = about 0.7; impurities A and B = about 0.8; impurity D = about 1.3.

System suitability Reference solution (d):

— *resolution*: minimum 1.3 between the peaks due to impurities C and A.

Limits:

— *sum of impurities A and B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity C*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity D*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 1.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Dextrin

To 1 g of the finely powdered substance to be examined add 20 mL of *ethanol (96 per cent) R* and heat under a reflux condenser. The substance dissolves completely.

Soluble starch, sulfite

Maximum 15 ppm.

Dissolve 6.7 g in 15.0 mL of *water R*, heating on a water-bath. Allow to cool and add 25 µL of *iodine solution R5*. The solution is yellow.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.500 g.

www.webofpharma.com

https://thuocngocanh.com/

◊ **Pyrogens** (2.6.8)

If intended for use in the manufacture of large-volume parental preparations without a further appropriate procedure for the removal of pyrogens, the competent authority may require that it comply with the test for pyrogens. Inject per kilogram of the rabbit's mass 10 mL of a solution in *water for injections R* containing 50 mg of the substance to be examined per millilitre.◊

ASSAY

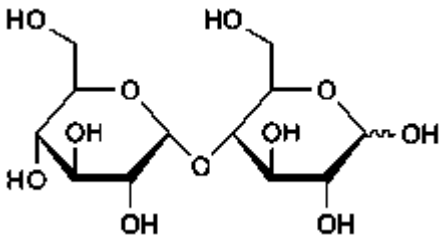
Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

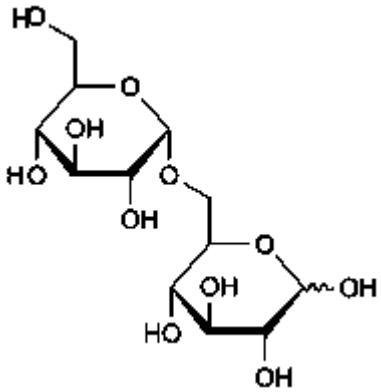
Calculate the percentage content of $C_6H_{12}O_6$ taking into account the assigned content of *glucose monohydrate CRS*.

IMPURITIES

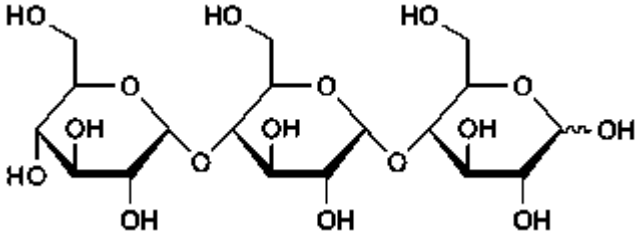
Specified impurities *A, B, C, D.*



A. 4-*O*-α-D-glucopyranosyl-D-glucopyranose (maltose),



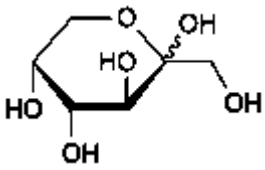
B. 6-*O*-α-D-glucopyranosyl-D-glucopyranose (isomaltose),



C. α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucopyranose (maltotriose),

www.webofpharma.com

https://thuocngocanh.com/



D. D-*arabino*-hex-2-ulopyranose (fructose).

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glucose Infusion

General Notices

Glucose Injection

Glucose Intravenous Infusion

DEFINITION

Glucose Infusion is a sterile solution containing Glucose or Glucose Monohydrate. It is supplied as a ready-to-use solution.

The infusion complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of glucose, $C_6H_{12}O_6$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution. Solutions containing the equivalent of 200 g per litre or more of glucose, $C_6H_{12}O_6$, may be not more than faintly yellow in colour.

IDENTIFICATION

A. Heat with *cupri-tartaric solution R1*. A red precipitate is produced.

B. The solution prepared as directed in the Assay is dextrorotatory.

TESTS

Acidity

pH, 3.5 to 6.5, Appendix V L, when determined on a solution diluted, if necessary, with *water for injections*, to contain not more than the equivalent of 5% w/v of glucose, $C_6H_{12}O_6$, and to which 0.30 mL of a saturated solution of *potassium chloride* has been added for each 100 mL of solution.

5-Hydroxymethylfurfural and related substances

Dilute a volume containing the equivalent of 1.0 g of glucose, $C_6H_{12}O_6$, to 250 mL with *water*. The *absorbance* of the resulting solution at the maximum at 284 nm is not more than 0.25, Appendix II B.

Bacterial endotoxins

The endotoxin limit concentration is 0.25 IU per mL, Appendix XIV C. Dilute infusions containing more than 5% w/v of Glucose with *water BET* to contain 5% w/v.

www.webofpharma.com

https://thietbiuocngocanh.com/

ASSAY

To a volume containing the equivalent of 2 g to 5 g of glucose, $C_6H_{12}O_6$, add 0.2 mL of 5M *ammonia* and sufficient *water* to produce 100 mL. Mix well, allow to stand for 30 minutes and determine the *optical rotation* in a 2-dm tube, Appendix V F. The observed rotation in degrees multiplied by 0.9477 represents the weight in g of glucose, $C_6H_{12}O_6$, in the volume taken for assay.

LABELLING

The strength is stated as the equivalent number of grams of glucose, $C_6H_{12}O_6$, per litre.

When Glucose Infusion is required as a diluent for Injections or Infusions of the Pharmacopoeia, Glucose Infusion (50 g per litre) shall be used.

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

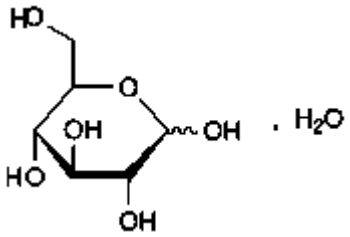
This text was updated in Ph. Eur. 11.1 (effective 01/04/2023)

Glucose Monohydrate[1]

General Notices

(Ph. Eur. monograph 0178)

NOTE: *The name Glucose was formerly used in the United Kingdom.*



$C_6H_{12}O_6,H_2O$ 198.2 *77938-63-7*

Preparations

Glucose Infusion

Oral Rehydration Salts

Potassium Chloride and Glucose Intravenous Infusion

Potassium Chloride, Sodium Chloride and Glucose Intravenous Infusion

Sodium Chloride and Glucose Intravenous Infusion

Ph Eur

DEFINITION

D-Glucopyranose monohydrate.

It is derived from starch.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

♦ CHARACTERS

www.webofpharma.com

https://thuocngocanh.com/

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).♦

IDENTIFICATION

First identification: ◊ *A*◊ *, B, E.*

◊ *Second identification: C, D.*◊

◊ A. Specific optical rotation (2.2.7): + 52.5 to + 53.3 (anhydrous substance).
Dissolve 10.0 g in 80 mL of *water R*, add 0.2 mL of *dilute ammonia R1*, allow to stand for 30 min and dilute to 100.0 mL with *water R*.◊

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

◊ C. Thin-layer chromatography (2.2.27).

Solvent mixture *water R*, *methanol R* (40:60 *V/V*).

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution Dissolve 10 mg of *glucose monohydrate CRS* in the solvent mixture and dilute to 20 mL with the solvent mixture.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *methanol R*, *anhydrous acetic acid R*, *methylene chloride R* (10:15:25:50 *V/V/V/V*); measure the volumes accurately since a slight excess of water produces cloudiness.

Application 2 µL; thoroughly dry the points of application.

Development A Over 3/4 of the plate.

Drying A In a current of warm air.

Development B Immediately, over 3/4 of the plate, after renewing the mobile phase.

Drying B In a current of warm air.

Detection Treat with a solution of 0.5 g of *thymol R* in a mixture of 5 mL of *sulfuric acid R* and 95 mL of *ethanol (96 per cent) R*; heat at 130 °C for 10 min.

www.webofpharma.com

https://thuocngocanh.com/

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve 5 g in *water R* and dilute to 10 mL with the same solvent. To 0.5 mL of the solution, add 0.2 g of *resorcinol R* and 9 mL of *dilute hydrochloric acid R* and heat on a water-bath for 2 min. No red colour develops.◊

E. Water (see Tests).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 10.0 g in *water R*.

Conductivity (*2.2.38*)

Maximum 20 $\mu S \cdot cm^{-1}$.

Dissolve 20.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 100.0 mL with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.330 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.330 g of *glucose monohydrate CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of the test solution to 250.0 mL with *water R*.

Reference solution (c) Dilute 25.0 mL of reference solution (b) to 200.0 mL with *water R*.

Reference solution (d) Dissolve 5 mg of *fructose R* (impurity D), 5 mg of *maltose monohydrate R* (impurity A) and 5 mg of *maltotriose R* (impurity C) in *water R* and dilute to 50 mL with the same solvent.

Column:

— *size*: *l* = 0.3 m, Ø = 7.8 mm;

— *stationary phase*: *strong cation-exchange resin (calcium form) R* (9 µm);

— *temperature*: 85 ± 1 °C.

Mobile phase Degassed *water for chromatography R*.

Flow rate 0.3 mL/min.

www.webofpharma.com

https://thuocngocanh.com/

Detection Refractometer maintained at a constant temperature (40 °C for example).

Injection 20 µL of the test solution and reference solutions (b), (c) and (d).

Run time 1.5 times the retention time of glucose.

Relative retention With reference to glucose (retention time = about 21 min): impurity C = about 0.7; impurities A and B = about 0.8; impurity D = about 1.3.

System suitability Reference solution (d):

— *resolution*: minimum 1.3 between the peaks due to impurities C and A.

Limits:

— *sum of impurities A and B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);

— *impurity C*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *impurity D*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 1.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Dextrin

To 1 g of the finely powdered substance to be examined add 20 mL of *ethanol (96 per cent) R* and heat under a reflux condenser. The substance dissolves completely.

Soluble starch, sulfite

Maximum 15 ppm.

Dissolve 7.4 g in 15.0 mL of *water R*, heating on a water-bath. Allow to cool and add 25 µL of *iodine solution R5*. The solution is yellow.

Water (*2.5.12*)

7.5 per cent to 9.5 per cent, determined on 0.250 g.

www.webofpharma.com

https://thuocngocanh.com/

◊ **Pyrogens** (*2.6.8*)

If intended for use in the manufacture of large-volume parenteral preparations without a further appropriate procedure for the removal of pyrogens, the competent authority may require that it comply with the test for pyrogens. Inject per kilogram of the rabbit's mass 10 mL of a solution in *water for injections R* containing 50 mg of the substance to be examined per millilitre.◊

ASSAY

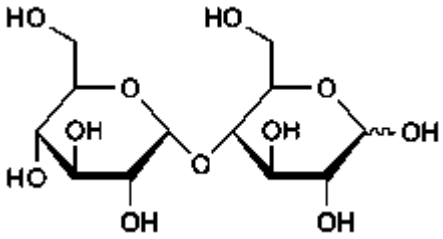
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution and reference solution (a).

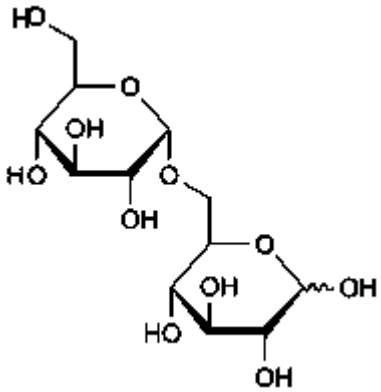
Calculate the percentage content of $C_6H_{12}O_6$ taking into account the assigned content of *glucose monohydrate CRS*.

IMPURITIES

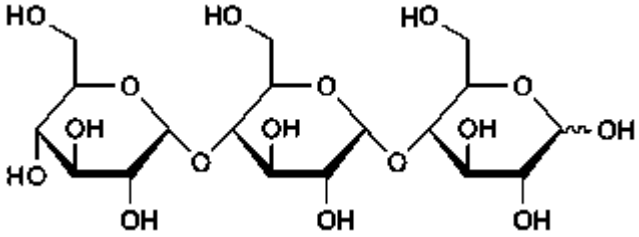
Specified impurities *A, B, C, D.*



A. 4-*O*-α-D-glucopyranosyl-D-glucopyranose (maltose),



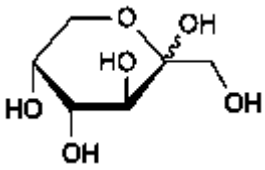
B. 6-*O*-α-D-glucopyranosyl-D-glucopyranose (isomaltose),



C. α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucopyranose (maltotriose),

www.webofpharma.com

https://thuocngocanh.com/



D. D-*arabino*-hex-2-ulopyranose (fructose).

Ph Eur

1 This monograph has undergone pharmacopoeial harmonisation. See chapter *5.8 Pharmacopoeial harmonisation*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

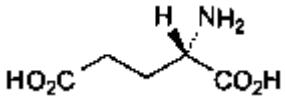
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Glutamic Acid

General Notices

(Ph. Eur. monograph 0750)



$C_5H_9NO_4$ 147.1 *56-86-0*

Action and use

Amino acid.

Ph Eur

DEFINITION

Glutamic acid contains not less than 98.5 per cent and not more than the equivalent of 100.5 per cent of (2*S*)-2-aminopentanedioic acid, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, freely soluble in boiling water, slightly soluble in cold water, practically insoluble in acetic acid, in acetone and in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Specific optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *glutamic acid CRS*. Examine the substances prepared as discs. If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum quantity of *water R*, evaporate to dryness at 60 °C and record new spectra using the residues.

C. Examine the chromatograms obtained in the test for ninhydrin-positive substances. The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

D. To 2.0 mL of solution S (see Tests) add 0.1 mL of *phenolphthalein solution R* and 3.0 mL to 3.5 mL of *1 M sodium hydroxide* to change the colour of the indicator to red. Add a mixture of 3 mL of *formaldehyde solution R*, 3 mL of *carbon dioxide-free water R* and 0.1 mL of *phenolphthalein solution R*, to which sufficient *1 M sodium hydroxide* has been added to produce a pink colour. The solution is decolourised. Add *1 M sodium hydroxide* until a red colour is produced. The total volume of *1 M sodium hydroxide* used is 4.0 mL to 4.7 mL.

TESTS

Solution S

Dissolve 5.00 g in *1 M hydrochloric acid* with gentle heating, and dilute to 50.0 mL with the same acid.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

+ 30.5 to + 32.5, determined on solution S and calculated with reference to the dried substance.

Ninhydrin-positive substances

Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel plate R*.

Test solution (a) Dissolve 0.10 g of the substance to be examined in 5 mL of *dilute ammonia R2* and dilute to 10 mL with *water R*.

Test solution (b) Dilute 1 mL of test solution (a) to 50 mL with *water R*.

Reference solution (a) Dissolve 10 mg of *glutamic acid CRS* in *water R* and dilute to 50 mL with the same solvent.

Reference solution (b) Dilute 5 mL of test solution (b) to 20 mL with *water R*.

Reference solution (c) Dissolve 10 mg of *glutamic acid CRS* and 10 mg of *aspartic acid CRS* in *water R* and dilute to 25 mL with the same solvent.

Apply to the plate 5 µL of each solution. Dry the plate in a current of air for 15 min. Develop over a path of 15 cm using a mixture of 20 volumes of *glacial acetic acid R*, 20 volumes of *water R* and 60 volumes of *butanol R*. Allow the plate to dry in air, spray with *ninhydrin solution R* and heat at 100-105 °C for 15 min. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows 2 clearly separated spots.

Chlorides (*2.4.4*)

Dissolve 0.25 g in 3 mL of *dilute nitric acid R* and dilute to 15 mL with *water R*. The solution, to which 1 mL of *water R* is added instead of *dilute nitric acid R*, complies with the limit test for chlorides (200 ppm).

Sulfates (*2.4.13*)

www.webofpharma.com

https://thietbiuocngocanh.com/

Dilute 5 mL of solution S to 15 mL with *distilled water R*. The solution complies with the limit test for sulfates (300 ppm).

Ammonium (*2.4.1*)

50 mg complies with limit test B for ammonium (200 ppm). Prepare the standard using 0.1 mL of *ammonium standard solution (100 ppm NH_4) R*.

Iron (*2.4.9*)

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers add 10 mL of *water R* and shake for 3 min. The aqueous layer complies with the limit test for iron (10 ppm).

Loss on drying (*2.2.32*)

Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.130 g in 50 mL of *carbon dioxide-free water R* with gentle heating. Cool. Using 0.1 mL of *bromothymol blue solution R1* as indicator, titrate with *0.1 M sodium hydroxide* until the colour changes from yellow to blue.

1 mL of *0.1 M sodium hydroxide* is equivalent to 14.71 mg of $C_5H_9NO_4$.

STORAGE

Protected from light.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glutaraldehyde Solution

General Notices

DEFINITION

Glutaraldehyde Solution is a dilution of Strong Glutaraldehyde Solution in a mixture of Purified Water and Ethanol (96 per cent).

In making Glutaraldehyde Solution, Ethanol (96 per cent) may be replaced by Industrial Methylated Spirit[1].

Content of glutaraldehyde, $C_5H_8O_2$

9.2 to 10.5% w/v.

IDENTIFICATION

A. Heat 5 mL with 10 mL of a solution containing 1 g of *hydroxylamine hydrochloride* and 2 g of *sodium acetate* on a water bath for 10 minutes, allow to cool and filter. The *melting point* of the residue, after washing with *water* and drying at 105°, is about 178°, Appendix V A.

B. To 1 mL add 2 mL of *ammoniacal silver nitrate solution* and mix gently for a few minutes. Silver is deposited.

TESTS

Ethanol content

50.0 to 60.0% v/v, Appendix VIII F.

ASSAY

Mix 10 mL with 100 mL of a 7% w/v solution of *hydroxylamine hydrochloride* previously neutralised to *bromophenol blue solution* with *1M sodium hydroxide VS* and allow to stand for 30 minutes. Add 20 mL of *petroleum spirit (boiling range, 40° to 60°)* and titrate with *1M sodium hydroxide VS* until the colour of the aqueous phase matches that of a 7% w/v solution of *hydroxylamine hydrochloride* previously neutralised to *bromophenol blue solution* with *1M sodium hydroxide VS*. Each mL of *1M sodium hydroxide VS* is equivalent to 50.05 mg of $C_5H_8O_2$.

1 The law and the statutory regulations governing the use of Industrial Methylated Spirit must be observed.

© Crown Copyright 2022

www.webofpharma.com

https://thietbiuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

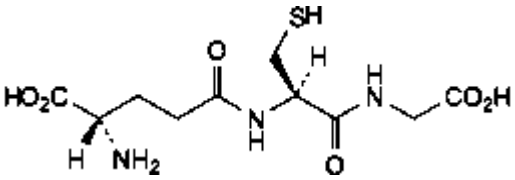
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glutathione

General Notices

(Ph. Eur. monograph 1670)



$C_{10}H_{17}N_3O_6S$ 307.3 *70-18-8*

Ph Eur

DEFINITION

L-γ-Glutamyl-L-cysteinylglycine.

Fermentation product.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder or colourless crystals.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *glutathione CRS*.

TESTS

Solution S

www.webofpharma.com

https://thuocngocanh.com/

Solution S

Dissolve 5.0 g in *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*)

-17.5 to -15.5 (dried substance).

Dissolve 1.0 g in *water R* and dilute to 25.0 mL with the same solvent.

Related substances

Capillary electrophoresis (*2.2.47*). *Prepare the solutions immediately before use.*

Internal standard solution (a) Dissolve 0.100 g of *phenylalanine R* in the electrolyte solution and dilute to 50.0 mL with the same solution.

Internal standard solution (b) Dilute 10.0 mL of internal standard solution (a) to 100.0 mL with the electrolyte solution.

Test solution (a) Dissolve 0.200 g of the substance to be examined in the electrolyte solution and dilute to 10.0 mL with the same solution.

Test solution (b) Dissolve 0.200 g of the substance to be examined in internal standard solution (b) and dilute to 10.0 mL with the same solution.

Reference solution (a) Dissolve 20.0 mg of the substance to be examined in internal standard solution (a) and dilute to 10.0 mL with the same solution.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 50.0 mL with the electrolyte solution.

Reference solution (c) Dissolve 0.200 g of the substance to be examined in 5 mL of the electrolyte solution. Add 1.0 mL of internal standard solution (a), 0.5 mL of a 2 mg/mL solution of *L-cysteine R* (impurity B) in the electrolyte solution, 0.5 mL of a 2 mg/mL solution of oxidised L-glutathione R (impurity C) in the electrolyte solution and 0.5 mL of a 2 mg/mL solution of *L-γ-glutamyl-L-cysteine R* (impurity D) in the electrolyte solution. Dilute to 10.0 mL with the electrolyte solution.

Capillary:

— *material*: uncoated fused silica;

— *size*: length to the detector cell = 0.5 m; total length = 0.6 m; Ø = 75 µm.

Temperature 25 °C.

Electrolyte solution Dissolve 1.50 g of *anhydrous sodium dihydrogen phosphate R* in 230 mL of *water R* and adjust to pH 1.80 with *phosphoric acid R*. Dilute to 250.0 mL with *water R*. Check the pH and, if necessary, adjust with *phosphoric acid R* or *dilute sodium hydroxide solution R*.

Detection Spectrophotometer at 200 nm.

www.webofpharma.com

https://thuocngocanh.com/

Preconditioning of a new capillary Rinse the new capillary before the first injection with *0.1 M hydrochloric acid* at 138 kPa for 20 min and with *water R* at 138 kPa for 10 min; for complete equilibration, condition the capillary with the electrolyte solution at 350 kPa for 40 min, and subsequently at a voltage of 20 kV for 60 min.

Preconditioning of the capillary Rinse the capillary with the electrolyte solution at 138 kPa for 40 min.

Between-run rinsing Rinse the capillary with *water R* at 138 kPa for 1 min, with *0.1 M sodium hydroxide* at 138 kPa for 2 min, with *water R* at 138 kPa for 1 min, with *0.1 M hydrochloric acid* at 138 kPa for 3 min and with the electrolyte solution at 138 kPa for 10 min.

Injection Test solutions (a) and (b), reference solutions (b) and (c) and the electrolyte solution (blank): under pressure (3.45 kPa) for 5 s.

Migration Apply a voltage of 20 kV.

Run time 45 min.

Relative migration With reference to the internal standard (about 14 min): impurity A = about 0.77; impurity B = about 1.04; impurity E = about 1.2; impurity C = about 1.26; impurity D = about 1.3.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to the internal standard and impurity B in the electropherogram obtained with reference solution (c); if necessary, increase the pH with *dilute sodium hydroxide solution R*;

— *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to glutathione in the electropherogram obtained with reference solution (c); if necessary, lower the pH with *phosphoric acid R*;

— check that in the electropherogram obtained with test solution (a) there is no peak with the same migration time as the internal standard (in such case correct the area of the phenylalanine peak).

Limits Test solution (b):

— *corrected areas*: divide all the peak areas by the corresponding migration times;

— *correction factors*: for the calculation of content, multiply the ratio of time-corrected peak areas of impurity and the internal standard by the corresponding correction factor: impurity B = 3.0; impurity D = 1.4;

— *impurity C*: not more than 1.5 times the ratio of the area of the peak due to glutathione to the area of the peak due to the internal standard in the electropherogram obtained with reference solution (b) (1.5 per cent);

— *impurity D*: not more than the ratio of the area of the peak due to glutathione to the area of the peak due to the internal standard in the electropherogram obtained with reference solution (b) (1.0 per cent);

— *impurities A, B, E*: for each impurity, not more than 0.5 times the ratio of the area of the peak due to glutathione to the area of the peak due to the internal standard in the electropherogram obtained with reference solution (b) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *any other impurity*: for each impurity, not more than 0.2 times the ratio of the area of the peak due to glutathione to the area of the peak due to the internal standard in the electropherogram obtained with reference solution (b) (0.2 per cent);

— *total*: not more than 2.5 times the ratio of the area of the peak due to glutathione to the area of the peak due to the internal standard in the electropherogram obtained with reference solution (b) (2.5 per cent);

— *disregard limit*: 0.05 times the ratio of the area of the peak due to glutathione to the area of the peak due to the internal standard in the electropherogram obtained with reference solution (b) (0.05 per cent).

Chlorides

Maximum 200 ppm.

Dissolve 0.5 g in 5 mL of *dilute nitric acid R* and dilute to 10 mL with the same solvent. Add 10 mL of *strong hydrogen peroxide solution R* and heat on a water-bath for 30 min. Cool and dilute to 50 mL with *water R*. Add 1 mL of *silver nitrate solution R2* and mix. Allow to stand for 5 min protected from light. Any opalescence in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 2 mL of *chloride standard solution (50 ppm Cl) R*. Examine the tubes laterally against a black background.

Sulfates (*2.4.13*)

Maximum 300 ppm.

Dilute 5 mL of solution S to 15 mL with *distilled water R*.

Ammonium (*2.4.1, Method B*)

Maximum 200 ppm, determined on 50 mg.

Prepare the standard using 0.1 mL of *ammonium standard solution (100 ppm NH_4) R*.

Iron (*2.4.9*)

Maximum 10 ppm.

In a separating funnel, dissolve 1.0 g in 10 mL of *dilute hydrochloric acid R*. Shake with 3 quantities, each of 10 mL, of *methyl isobutyl ketone R1*, shaking for 3 min each time. To the combined organic layers, add 10 mL of *water R* and shake for 3 min. The aqueous layer complies with the test.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

www.webofpharma.com

https://thietbiuocngocanh.com/

In a ground-glass-stoppered flask, dissolve 0.500 g of the substance to be examined and 2 g of *potassium iodide R* in 50 mL of *water R*. Cool the solution in iced water and add 10 mL of *hydrochloric acid R1* and 20.0 mL of *0.05 M iodine*. Stopper the flask and allow to stand in the dark for 15 min. Titrate with *0.1 M sodium thiosulfate* using 1 mL of *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration.

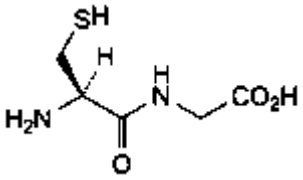
1 mL of *0.05 M iodine* is equivalent to 30.73 mg of $C_{10}H_{17}N_3O_6S$.

STORAGE

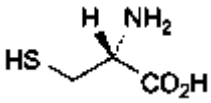
Protected from light.

IMPURITIES

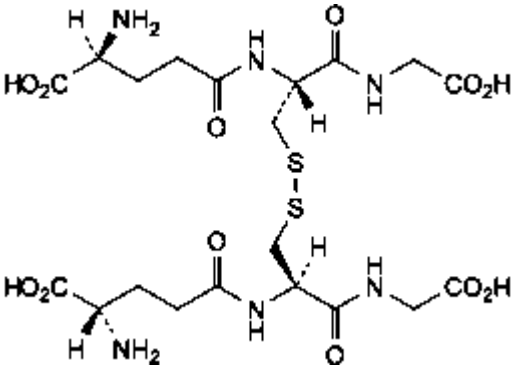
Specified impurities *A, B, C, D, E.*



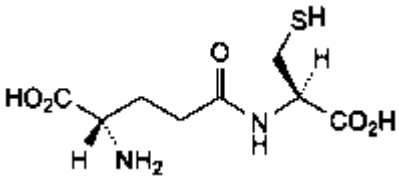
A. L-cysteinylglycine,



B. (2*R*)-2-amino-3-sulfanylpropanoic acid (cysteine),



C. bis(L-γ-glutamyl-L-cysteinylglycine) disulfide (L-glutathione oxidised),



D. L-γ-glutamyl-L-cysteine,

www.webofpharma.com

https://thietbiuocngocanh.com/

E. unknown structure (product of degradation).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol (85 per cent)

General Notices

(Ph. Eur. monograph 0497)

Ph Eur

DEFINITION

Aqueous solution of propane-1,2,3-triol.

Content

83.5 per cent *m/m* to 88.5 per cent *m/m* of propane-1,2,3-triol ($C_3H_8O_3$; M_r 92.1).

CHARACTERS

Appearance

Clear, colourless or almost colourless, very hygroscopic, syrupy liquid, unctuous to the touch.

Solubility

Miscible with water and with ethanol (96 per cent), slightly soluble in acetone, practically insoluble in fatty oils and in essential oils.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Refractive index (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of glycerol (85 per cent)*.

C. Relative density (2.2.5): 1.221 to 1.232.

TESTS

Solution S

Dilute 117.6 g to 200.0 mL with *carbon dioxide-free water R*.

Appearance of solution

www.webofpharma.com

https://thuocngocanh.com/

Appearance of solution

Solution S is clear (*2.2.1*). Dilute 10 mL of solution S to 25 mL with *water R*. The solution is colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 50 mL of solution S add 0.5 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Refractive index (*2.2.6*)

1.449 to 1.455.

Aldehydes

Maximum 10 ppm.

Place 7.5 mL of solution S in a ground-glass-stoppered flask and add 7.5 mL of *water R* and 1.0 mL of *decolorised pararosaniline solution R*. Close the flask and allow to stand for 1 h at a temperature of 25 ± 1 °C. The absorbance (*2.2.25*) of the solution measured at 552 nm is not greater than that of a standard prepared at the same time and in the same manner using 7.5 mL of *formaldehyde standard solution (5 ppm CH_2O) R* and 7.5 mL of *water R*. The test is not valid unless the standard is pink.

Esters

Add 10.0 mL of *0.1 M sodium hydroxide* to the final solution obtained in the test for acidity or alkalinity. Boil under a reflux condenser for 5 min. Cool. Add 0.5 mL of *phenolphthalein solution R* and titrate with *0.1 M hydrochloric acid*. Not less than 8.0 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Impurity A and related substances

Gas chromatography (*2.2.28*).

Test solution Dilute 10.0 mL of solution S to 100.0 mL with *water R*.

Reference solution (a) Dilute 11.8 g of *glycerol (85 per cent) R1* to 20.0 mL with *water R*. Dilute 10.0 mL of the solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 1.000 g of *diethylene glycol R* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with reference solution (a). Dilute 1.0 mL of this solution to 20.0 mL with reference solution (a).

Reference solution (d) Mix 1.0 mL of the test solution and 5.0 mL of reference solution (b) and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (e) Dilute 5.0 mL of reference solution (b) to 100.0 mL with *water R*.

Column:

— *size*: *l* = 30 m, Ø = 0.53 mm;

www.webofpharma.com

https://thietbiuocngocanh.com/

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R*.

Carrier gas *helium for chromatography R*.

Split ratio 1:10.

Linear velocity 38 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0	100
	0 - 16	100 → 220
	16 - 20	220
Injection port		220
Detector		250

Detection Flame ionisation.

Injection 0.5 µL.

Elution order Impurity A, glycerol.

System suitability Reference solution (d):

— *resolution*: minimum 7.0 between the peaks due to impurity A and glycerol.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *any other impurity with a retention time less than the retention time of glycerol*: not more than the area of the peak due to impurity A in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *total of all impurities with retention times greater than the retention time of glycerol*: not more than 5 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.05 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (e) (0.05 per cent).

Halogenated compounds

Maximum 30 ppm.

www.webofpharma.com

https://thuocngocanh.com/

To 10 mL of solution S add 1 mL of *dilute sodium hydroxide solution R*, 5 mL of *water R* and 50 mg of *halogen-free nickel-aluminium alloy R*. Heat on a water-bath for 10 min, allow to cool and filter. Rinse the flask and the filter with *water R* until 25 mL of filtrate is obtained. To 5 mL of the filtrate add 4 mL of *ethanol (96 per cent) R*, 2.5 mL of *water R*, 0.5 mL of *nitric acid R* and 0.05 mL of *silver nitrate solution R2* and mix. Allow to stand for 2 min. Any opalescence in the solution is not more intense than that in a standard prepared at the same time by mixing 7.0 mL of *chloride standard solution (5 ppm Cl) R*, 4 mL of *ethanol (96 per cent) R*, 0.5 mL of *water R*, 0.5 mL of *nitric acid R* and 0.05 mL of *silver nitrate solution R2*.

Sugars

To 10 mL of solution S add 1 mL of *dilute sulfuric acid R* and heat on a water-bath for 5 min. Add 3 mL of an 85 mg/mL solution of *sodium hydroxide R* in *carbon dioxide-free water R*, mix and add dropwise 1 mL of freshly prepared *copper sulfate solution R*. The solution is clear and blue. Continue heating on the water-bath for 5 min. The solution remains blue and no precipitate is formed.

Chlorides (*2.4.4*)

Maximum 10 ppm.

Dilute 1 mL of solution S to 15 mL with *water R*. Prepare the standard using 1 mL of *chloride standard solution (5 ppm Cl) R* diluted to 15 mL with *water R*.

Water (*2.5.12*)

12.0 per cent to 16.0 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.01 per cent, determined on 5.0 g after heating to boiling and ignition.

ASSAY

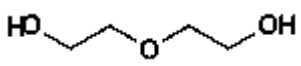
Thoroughly mix 0.075 g with 45 mL of *water R*. Add 25.0 mL of a mixture of 1 volume of *0.1 M sulfuric acid* and 20 volumes of *0.1 M sodium periodate*. Allow to stand protected from light for 15 min. Add 5.0 mL of a 500 g/L solution of *ethylene glycol R* and allow to stand protected from light for 20 min. Using 0.5 mL of *phenolphthalein solution R* as indicator, titrate with *0.1 M sodium hydroxide*. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 9.21 mg of $C_3H_8O_3$.

STORAGE

In an airtight container.

IMPURITIES

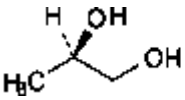


A. 2,2′-oxydi(ethan-1-ol) (diethylene glycol),

www.webofpharma.com

https://thuocngocanh.com/

B. ethane-1,2-diol (ethylene glycol),



and enantiomer

C. (2*RS*)-propane-1,2-diol (propylene glycol).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

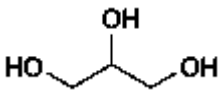
https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol

General Notices

(Ph. Eur. Monograph 0496)



$C_3H_8O_3$ 92.1 *56-81-5*

Action and use

Lubricant; laxative.

Preparations

Glycerol Eye Drops

Glycerol Suppositories

Ph Eur

DEFINITION

Propane-1,2,3-triol.

Content

98.0 per cent *m/m* to 101.0 per cent *m/m* (anhydrous substance).

CHARACTERS

Appearance

Clear, colourless or almost colourless, very hygroscopic, syrupy liquid, unctuous to the touch.

Solubility

Miscible with water and with ethanol (96 per cent), slightly soluble in acetone, practically insoluble in fatty oils and in essential oils.

IDENTIFICATION

First identification: A, B.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: A, C.

A. Refractive index (see Tests).

B. Infrared absorption spectrophotometry (2.2.24).

Preparation To 5 mL add 1 mL of *water R* and mix carefully.

Comparison *Ph. Eur. reference spectrum of glycerol (85 per cent)*.

C. Relative density (2.2.5): 1.258 to 1.268.

TESTS

Solution S

Dilute 100.0 g to 200.0 mL with *carbon dioxide-free water R*.

Appearance of solution

Solution S is clear (2.2.1). Dilute 10 mL of solution S to 25 mL with *water R*. The solution is colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 50 mL of solution S add 0.5 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 0.2 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to pink.

Refractive index (2.2.6)

1.470 to 1.475.

Aldehydes

Maximum 10 ppm.

Place 7.5 mL of solution S in a ground-glass-stoppered flask and add 7.5 mL of *water R* and 1.0 mL of *decolorised pararosaniline solution R*. Close the flask and allow to stand for 1 h at a temperature of 25 ± 1 °C. The absorbance (2.2.25) of the solution measured at 552 nm is not greater than that of a standard prepared at the same time and in the same manner using 7.5 mL of *formaldehyde standard solution (5 ppm CH_2O) R* and 7.5 mL of *water R*. The test is not valid unless the standard is pink.

Esters

Add 10.0 mL of *0.1 M sodium hydroxide* to the final solution obtained in the test for acidity or alkalinity. Boil under a reflux condenser for 5 min. Cool. Add 0.5 mL of *phenolphthalein solution R* and titrate with *0.1 M hydrochloric acid*. Not less than 8.0 mL of *0.1 M hydrochloric acid* is required to change the colour of the indicator.

Impurity A and related substances

Gas chromatography (2.2.28).

www.webofpharma.com

https://thuocngocanh.com/

Test solution Dilute 10.0 mL of solution S to 100.0 mL with *water R*.

Reference solution (a) Dilute 10.0 g of *glycerol R1* to 20.0 mL with *water R*. Dilute 10.0 mL of the solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 1.000 g of *diethylene glycol R* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with reference solution (a). Dilute 1.0 mL of this solution to 20.0 mL with reference solution (a).

Reference solution (d) Mix 1.0 mL of the test solution and 5.0 mL of reference solution (b) and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (e) Dilute 5.0 mL of reference solution (b) to 100.0 mL with *water R*.

Column:

— *size*: *l* = 30 m, Ø = 0.53 mm;

— *stationary phase*: *cyanopropyl(3)phenyl(3)methyl(94)polysiloxane R*.

Carrier gas *helium for chromatography R*.

Split ratio 1:10.

Linear velocity 38 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0	100
	0 - 16	100 → 220
	16 - 20	220
Injection port		220
Detector		250

Detection Flame ionisation.

Injection 0.5 µL.

Elution order Impurity A, glycerol.

System suitability Reference solution (d):

— *resolution*: minimum 7.0 between the peaks due to impurity A and glycerol.

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *any other impurity with a retention time less than the retention time of glycerol*: not more than the area of the peak due to impurity A in the chromatogram obtained with reference solution (c) (0.1 per cent);

— *total of all impurities with retention times greater than the retention time of glycerol*: not more than 5 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *disregard limit*: 0.05 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (e) (0.05 per cent).

Halogenated compounds

Maximum 35 ppm.

To 10 mL of solution S add 1 mL of *dilute sodium hydroxide solution R*, 5 mL of *water R* and 50 mg of *halogen-free nickel-aluminium alloy R*. Heat on a water-bath for 10 min, allow to cool and filter. Rinse the flask and the filter with *water R* until 25 mL of filtrate is obtained. To 5 mL of the filtrate add 4 mL of *ethanol (96 per cent) R*, 2.5 mL of *water R*, 0.5 mL of *nitric acid R* and 0.05 mL of *silver nitrate solution R2* and mix. Allow to stand for 2 min. Any opalescence in the solution is not more intense than that in a standard prepared at the same time by mixing 7.0 mL of *chloride standard solution (5 ppm Cl) R*, 4 mL of *ethanol (96 per cent) R*, 0.5 mL of *water R*, 0.5 mL of *nitric acid R* and 0.05 mL of *silver nitrate solution R2*.

Sugars

To 10 mL of solution S add 1 mL of *dilute sulfuric acid R* and heat on a water-bath for 5 min. Add 3 mL of an 85 mg/mL solution of *sodium hydroxide R* in *carbon dioxide-free water R*, mix and add dropwise 1 mL of freshly prepared *copper sulfate solution R*. The solution is clear and blue. Continue heating on the water-bath for 5 min. The solution remains blue and no precipitate is formed.

Chlorides (*2.4.4*)

Maximum 10 ppm.

Dilute 1 mL of solution S to 15 mL with *water R*. Prepare the standard using 1 mL of *chloride standard solution (5 ppm Cl) R* diluted to 15 mL with *water R*.

Water (*2.5.12*)

Maximum 2.0 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*)

Maximum 0.01 per cent, determined on 5.0 g after heating to boiling and ignition.

ASSAY

www.webofpharma.com

https://thietbiuocngocanh.com/

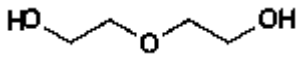
Thoroughly mix 0.075 g with 45 mL of *water R*. Add 25.0 mL of a mixture of 1 volume of *0.1 M sulfuric acid* and 20 volumes of *0.1 M sodium periodate*. Allow to stand protected from light for 15 min. Add 5.0 mL of a 500 g/L solution of *ethylene glycol R* and allow to stand protected from light for 20 min. Using 0.5 mL of *phenolphthalein solution R* as indicator, titrate with *0.1 M sodium hydroxide*. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 9.21 mg of $C_3H_8O_3$.

STORAGE

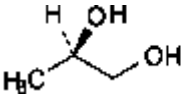
In an airtight container.

IMPURITIES



A. 2,2′-oxydi(ethan-1-ol) (diethylene glycol),

B. ethane-1,2-diol (ethylene glycol),



C. (2*RS*)-propane-1,2-diol (propylene glycol).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Dibehenate

General Notices

(Ph. Eur. monograph 1427)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols, obtained by esterification of *Glycerol (0496)* with behenic (docosanoic) acid.

Content

— *monoacylglycerols*: 15.0 per cent to 23.0 per cent;

— *diacylglycerols*: 40.0 per cent to 60.0 per cent;

— *triacylglycerols*: 21.0 per cent to 35.0 per cent.

CHARACTERS

Appearance

Hard, waxy mass, or powder or white or almost white, unctuous flakes.

Solubility

Practically insoluble in water, soluble in methylene chloride, partly soluble in hot ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 65 °C to 77 °C.

B. Composition of fatty acids (see Tests).

C. It complies with the assay (content of diacylglycerols).

TESTS

Acid value (*2.5.1*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 4.0, determined on 1.0 g using a mixture of equal volumes of *ethanol (96 per cent) R* and *toluene R* as solvent and with gentle heating.

Iodine value (*2.5.4, Method A*)

Maximum 3.0.

Saponification value (*2.5.6*)

145 to 165.

Carry out the titration with heating.

Free glycerol

Maximum 1.0 per cent, determined as described under Assay.

Composition of fatty acids

Gas chromatography (*2.4.22, Method C*) with the following modifications. Raise the temperature of the column to 240 °C and use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty acid fraction of the substance:

— *palmitic acid*: maximum 3.0 per cent;

— *stearic acid*: maximum 5.0 per cent;

— *arachidic acid*: maximum 10.0 per cent;

— *behenic acid*: minimum 83.0 per cent;

— *erucic acid*: maximum 3.0 per cent;

— *lignoceric acid*: maximum 3.0 per cent.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g. Use *pyridine R* as the solvent.

Total ash (*2.4.16*)

Maximum 0.1 per cent, determined on 1.00 g.

ASSAY

Size-exclusion chromatography (*2.2.30*).

Stock solution Place 0.100 g of *glycerol R* in a flask and dilute to 25.0 mL with *tetrahydrofuran R*.

www.webofpharma.com

https://thuocngocanh.com/

Test solution In a 15 mL flask, weigh 0.200 g (*m*) of the substance to be examined and add 5.0 mL of *tetrahydrofuran R*. Heat gently, at about 35 °C, and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (*M*); use immediately.

Reference solutions Into four 15 mL flasks, introduce respectively 0.25 mL, 0.5 mL, 1.0 mL and 2.5 mL of the stock solution and add 5.0 mL of *tetrahydrofuran R*. Weigh each flask and calculate the concentration of glycerol in milligrams per gram of each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

Flow rate 1 mL/min.

Detection Differential refractive index.

Injection 40 µL; when injecting the test solution, maintain the flask at about 35 °C to avoid precipitation.

Relative retention With reference to glycerol (retention time = about 15 min): triacylglycerols = about 0.73; diacylglycerols = about 0.76; monoacylglycerols = about 0.82.

Calculations:

— *free glycerol*: from the calibration curve obtained with the reference solutions, determine the concentration (*C*) in milligrams per gram in the test solution and calculate the percentage content (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 340}{561.1}$$

I_A = acid value;

— *monoacylglycerols*: calculate the percentage content of monoacylglycerols using the following expression:

$$\left[\frac{X}{X+Y+Z}(100 - A - B)\right] - D$$

A = percentage content of free glycerol (see Tests);

B = percentage content of water (see Tests);

D = percentage content of free fatty acids;

X = area of the peak due to monoacylglycerols;

Y = area of the peak due to diacylglycerols;

www.webofpharma.com

https://thuocngocanh.com/

Z = area of the peak due to triacylglycerols;

— *diacylglycerols*: calculate the percentage content of diacylglycerols using the following expression:

$$\frac{Y}{X+Y+Z}(100 - A - B)$$

— *triacylglycerols*: calculate the percentage content of triacylglycerols using the following expression:

$$\frac{Z}{X+Y+Z}(100 - A - B)$$

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Distearate

General Notices

(Ph. Eur. monograph 1428)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of diacylglycerols, mainly distearoylglycerol, together with variable quantities of mono- and triacylglycerols. It is obtained by partial glycerolysis of vegetable oils containing triacylglycerols of palmitic (hexadecanoic) and stearic (octadecanoic) acids or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

Content

— *monoacylglycerols*: 8.0 per cent to 22.0 per cent;

— *diacylglycerols*: 40.0 per cent to 60.0 per cent;

— *triacylglycerols*: 25.0 per cent to 35.0 per cent.

CHARACTERS

Appearance

Hard, waxy mass or powder, or white or almost white, unctuous flakes.

Solubility

Practically insoluble in water, soluble in methylene chloride, partly soluble in hot ethanol (96 per cent).

IDENTIFICATION

A. Melting point (*2.2.14*): 50 °C to 60 °C (types I and II), 50 °C to 70 °C (type III).

B. Composition of fatty acids (see Tests) according to the type stated on the label.

C. It complies with the limits of the assay (diacylglycerol content).

TESTS

Acid value (*2.5.1*)

www.webofpharma.com

https://thuocngocanh.com/

Maximum 6.0, determined on 1.0 g.

Use a mixture of equal volumes of *ethanol (96 per cent) R* and *toluene R* as solvent and heat gently.

Iodine value (*2.5.4, Method A*)

Maximum 3.0.

Saponification value (*2.5.6*)

165 to 195, determined on 2.0 g. Carry out the titration with heating.

Free glycerol

Maximum 1.0 per cent, determined as described under Assay.

Composition of fatty acids (*2.4.22, Method C*)

Use the mixture of calibrating substances in Table 2.4.22.-1.

Composition of the fatty-acid fraction of the substance:

Glycerol distearate	Composition of fatty acids
Type I	*Stearic acid*: 40.0 per cent to 60.0 per cent *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent
Type II	*Stearic acid*: 60.0 per cent to 80.0 per cent *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent
Type III	*Stearic acid*: 80.0 per cent to 99.0 per cent *Sum of the contents of palmitic and stearic acids*: minimum 96.0 per cent

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g. Use *pyridine R* as the solvent.

Total ash (*2.4.16*)

Maximum 0.1 per cent.

ASSAY

Size-exclusion chromatography (*2.2.30*).

Test solution Into a 15 mL flask, weigh 0.200 g (*m*) of the substance to be examined. Add 5.0 mL of *tetrahydrofuran R* and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

www.webofpharma.com

https://thuocngocanh.com/

Reference solutions Into three 15 mL flasks, respectively weigh 2.0 mg, 5.0 mg and 10.0 mg of *glycerol R* and add 5.0 mL of *tetrahydrofuran R* to each flask. Into a 4th flask, weigh 2.0 mg of *glycerol R* and add 10.0 mL of *tetrahydrofuran R*. Weigh the flasks again and calculate the concentration of glycerol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

Flow rate 1 mL/min.

Detection Differential refractometer.

Injection 40 µL.

Relative retention With reference to glycerol (retention time = about 15 min): triacylglycerols = about 0.75; diacylglycerols = about 0.80; monoacylglycerols and free fatty acids = about 0.85.

Calculations:

— *free glycerol*: from the calibration curve obtained with the reference solutions, determine the concentration (*C*) in milligrams per gram in the test solution and calculate the percentage content (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 340}{561.1}$$

I_A = acid value;

— *monoacylglycerols*: calculate the percentage content of monoacylglycerols using the following expression:

$$\left[\frac{x}{x+y+z}(100 - A - B)\right] - D$$

B = percentage content of water (see Tests);

X = area of the peak due to monoacylglycerols and free fatty acids;

Y = area of the peak due to diacylglycerols;

Z = area of the peak due to triacylglycerols;

— *diacylglycerols*: calculate the percentage content of diacylglycerols using the following expression:

www.webofpharma.com

https://thuocngocanh.com/

$$\frac{y}{x+y+z}(100 - A - B)$$

— *triacylglycerols*: calculate the percentage content of triacylglycerols using the following expression:

$$\frac{z}{x+y+z}(100 - A - B)$$

LABELLING

The label states the type of glycerol distearate.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Eye Drops

General Notices

DEFINITION

Glycerol Eye Drops are a sterile solution of Glycerol in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of glycerol, $C_3H_8O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix 1 mL of the eye drops with 0.5 mL of *nitric acid* and superimpose 0.5 mL of *potassium dichromate solution*. A blue ring develops at the interface of the liquids, which does not diffuse into the lower layer within 10 minutes.

TESTS

Acidity or alkalinity

pH, 4.5 to 7.5, Appendix V L.

ASSAY

Dilute a suitable volume of the eye drops with sufficient *water* to produce a solution containing 3% w/v of Glycerol. To 5 mL add 150 mL of *water* and neutralise with *0.1M sodium hydroxide VS*, using *bromocresol purple solution* as indicator. Add 1.6 g of *sodium periodate* and allow to stand protected from light for 15 minutes. Add 3 mL of *propan-1,2-diol*, shake, allow to stand protected from light for 5 minutes and titrate with *0.1M sodium hydroxide VS*. Each mL of *0.1M sodium hydroxide VS* is equivalent to 9.21 mg of $C_3H_8O_3$.

STORAGE

Glycerol Eye Drops should be protected from light.

Strengths available

Eye Drops containing 10, 20, 30 and 50% w/v of glycerol are available.

© Crown Copyright 2022

www.webofpharma.com

https://thietbiuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

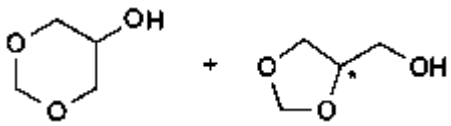
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Formal

General Notices

(Ph. Eur. monograph 1671)



$C_4H_8O_3$ 104.1

Ph Eur

DEFINITION

Mixture of 1,3-dioxan-5-ol and (1,3-dioxolan-4-yl)methanol.

CHARACTERS

Appearance

Clear, colourless liquid.

Solubility

Miscible with water and with ethanol (96 per cent).

IDENTIFICATION

A. Relative density (see Tests).

B. Refractive index (see Tests).

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *glycerol formal CRS*.

TESTS

Appearance

The substance to be examined is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

www.webofpharma.com

https://thuocngocanh.com/

4.0 to 6.5.

Dilute 1 mL to 10 mL with *carbon dioxide-free water R*.

Relative density (*2.2.5*)

1.210 to 1.220.

Refractive index (*2.2.6*)

1.445 to 1.455.

Peroxide value (*2.5.5*)

Maximum 15.

Formaldehyde

Maximum 200 ppm.

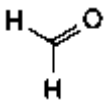
Dilute 0.250 g to 10 mL with *water R*. Add 2.0 mL of *acetylacetone reagent R2*, mix and heat on a water-bath at 60 °C for 20 min. Cool and dilute to 20.0 mL with *water R*. The absorbance (*2.2.25*) of the solution measured at 412 nm is not greater than that of a standard prepared at the same time and in the same manner using 5.0 mL of a dilution of *formaldehyde solution R* containing 10 µg of formaldehyde (CH_2O) per millilitre.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 5.000 g.

IMPURITIES

Specified impurities *A*.



A. formaldehyde.

STORAGE

Under nitrogen, in an airtight container.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thietbiuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Mono-oleate

General Notices

(Ph. Eur. monograph 1430

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of monoacylglycerols, mainly mono-oleoylglycerol, together with variable quantities of di- and triacylglycerols. It is defined by the nominal content of monoacylglycerols and obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of oleic ((9*Z*)-octadec-9-enoic) acid or by esterification of glycerol by oleic acid, this fatty acid being of vegetable or animal origin. A suitable antioxidant may be added.

Content

	Nominal content of acylglycerol (per cent)		
	40	**60**	**90**
Monoacylglycerols	32.0 - 52.0	55.0 - 65.0	90.0 - 101.0
Diacylglycerols	30.0 - 50.0	15.0 - 35.0	< 10.0
Triacylglycerols	5.0 - 20.0	2.0 - 10.0	< 2.0

CHARACTERS

Appearance

Amber, oily liquid which may be partially solidified at room temperature.

Solubility

Practically insoluble in water, freely soluble in methylene chloride.

IDENTIFICATION

A. Iodine value (see Tests).

B. Thin-layer chromatography (2.2.27).

www.webofpharma.com

https://thietbiuocngocanh.com/

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20 mL with the same solvent.

Reference solution Dissolve 1.0 g of *glycerol mono-oleate CRS* in *methylene chloride R* and dilute to 20 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine B R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The spots in the chromatogram obtained with the test solution are similar in position to those in the chromatogram obtained with the reference solution.

C. It complies with the limits of the assay (monoacylglycerol content).

TESTS

Acid value (*2.5.1*)

Maximum 6.0, determined on 1.0 g.

Iodine value (*2.5.4, Method A*)

65.0 to 95.0.

Peroxide value (*2.5.5, Method A*)

Maximum 12.0, determined on 2.0 g.

Saponification value (*2.5.6*)

150 to 175, determined on 2.0 g.

Free glycerol

Maximum 6.0 per cent, determined as described in the assay.

Composition of fatty acids (*2.4.22, Method C*)

Composition of the fatty acid fraction of the substance:

— *palmitic acid*: maximum 12.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *oleic acid*: minimum 60.0 per cent;

— *linoleic acid*: maximum 35.0 per cent;

— *linolenic acid*: maximum 2.0 per cent;

— *arachidic acid*: maximum 2.0 per cent;

— *eicosenoic acid*: maximum 2.0 per cent.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g. Use as the solvent a mixture of equal volumes of *anhydrous methanol R* and *methylene chloride R*.

Total ash (2.4.16)

Maximum 0.1 per cent.

ASSAY

Size-exclusion chromatography (2.2.30).

Test solution Into a 15 mL flask, weigh about 0.2 g (*m*), to the nearest 0.1 mg. Add 5 mL of *tetrahydrofuran R* and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

Reference solutions Into four 15 mL flasks, respectively weigh, to the nearest 0.1 mg, about 2.5 mg, 5 mg, 10 mg and 20 mg of *glycerol R*. Add 5 mL of *tetrahydrofuran R* and shake until well mixed. Weigh the flasks again and calculate the concentration of glycerol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

Flow rate 1 mL/min.

Detection Differential refractometer.

Injection 40 µL.

Relative retention With reference to glycerol (retention time = about 15.6 min): triacylglycerols = about 0.76; diacylglycerols = about 0.79; monoacylglycerols = about 0.85.

Calculations:

www.webofpharma.com

https://thietbiuocngocanh.com/

— *free glycerol*: from the calibration curve obtained with the reference solutions determine the concentration of glycerol (*C*) in milligrams per gram in the test solution and calculate the percentage content of free glycerol (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 282}{56.11 \times 10}$$

I_A = acid value (see Tests);

282 = rounded molar mass of oleic acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

— *monoacylglycerols*: calculate the percentage content of monoacylglycerols using the following expression:

$$\left[\frac{X}{X+Y+Z}\ (100 - A - B)\right] - D$$

A = percentage content of free glycerol;

B = percentage content of water (see Tests);

D = percentage content of free fatty acids;

X = area of the peak due to monoacylglycerols and free fatty acids;

Y = area of the peak due to diacylglycerols;

Z = area of the peak due to triacylglycerols.

— *diacylglycerols*: calculate the percentage content of diacylglycerols using the following expression:

$$\frac{Y}{X+Y+Z}\ (100 - A - B)$$

— *triacylglycerols*: calculate the percentage content of triacylglycerols using the following expression:

$$\frac{Z}{X+Y+Z}\ (100 - A - B)$$

STORAGE

www.webofpharma.com

https://thietbiuocngocanh.com/

In an airtight container, protected from light.

LABELLING

The label states the nominal content of monoacylglycerol.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Monocaprylate

General Notices

(Ph. Eur. monograph 2213)

Ph Eur

DEFINITION

Mixture of monoacylglycerols, mainly mono-*O*-octanoylglycerol, containing variable quantities of di- and triacylglycerols, obtained by direct esterification of glycerol with caprylic (octanoic) acid, followed by a distillation step in the case of glycerol monocaprylate (type II).

Content

— *glycerol monocaprylate (type I)*:

— *monoacylglycerols*: 45.0 per cent to 75.0 per cent;

— *diacylglycerols*: 20.0 per cent to 50.0 per cent;

— *triacylglycerols*: maximum 10.0 per cent;

— *glycerol monocaprylate (type II)*:

— *monoacylglycerols*: minimum 80.0 per cent;

— *diacylglycerols*: maximum 20.0 per cent;

— *triacylglycerols*: maximum 5.0 per cent.

CHARACTERS

Appearance

Colourless or slightly yellow, oily liquid or soft mass.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent) and freely soluble in methylene chloride.

IDENTIFICATION

A. Composition of fatty acids (see Tests).

B. It complies with the limits of the assay (monoacylglycerols).

www.webofpharma.com

https://thietbiuocngocanh.com/

TESTS

Acid value (2.5.1)

Maximum 3.0.

Composition of fatty acids (2.4.22, Method C)

Use the mixture of calibrating substances in Table 2.4.22.-2.

Composition of the fatty acid fraction of the substance:

— *caproic acid*: maximum 1.0 per cent;

— *caprylic acid*: minimum 90.0 per cent;

— *capric acid*: maximum 10.0 per cent;

— *lauric acid*: maximum 1.0 per cent;

— *myristic acid*: maximum 0.5 per cent.

Free glycerol

Maximum 3.0 per cent.

Dissolve 1.20 g in 25.0 mL of *methylene chloride R*. Heat to about 50 °C then allow to cool. Add 100 mL of *water R*. Shake and add 25.0 mL of *periodic acetic acid solution R*. Shake again and allow to stand for 30 min. Add 40 mL of a 75 g/L solution of *potassium iodide R* and allow to stand for 1 min. Add 1 mL of *starch solution R*. Titrate with *0.1 M sodium thiosulfate* until the aqueous phase becomes colourless. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 2.3 mg of glycerol.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g.

Total ash (2.4.16)

Maximum 0.5 per cent.

ASSAY

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution To 0.25 g of the substance to be examined, add 5.0 mL of *tetrahydrofuran R* and shake to dissolve.

Reference solution (a) To 0.25 g of *glycerol monocaprylate CRS*, add 5.0 mL of *tetrahydrofuran R* and shake to dissolve.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) To 50 mg of *glycerol 1-octanoate R* and 50 mg of *glycerol 1-decanoate R*, add 2.5 mL of *tetrahydrofuran R* and shake to dissolve.

Column:

— *size*: *l* = 10 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.3 mL/min.

Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 3	60
	3 - 38	60 → 340
	38 - 50	340
Injection port		350
Detector		370

Detection Flame ionisation.

Injection 1 µL.

Identification of peaks Use the chromatogram supplied with *glycerol monocaprylate CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to mono-, di- and triacylglycerols.

System suitability Reference solution (b):

— *resolution*: minimum 5 between the peaks due to glycerol 1-octanoate and glycerol 1-decanoate.

For the calculation of the contents of mono-, di- and triacylglycerols, disregard the peaks with a retention time less than that of the monoacylglycerols, which are due to impurities of the solvent and to the free fatty acids.

Calculate the percentage content of free fatty acids (*C*) using the following expression:

$$\frac{I_A \times 144}{561.1}$$

I_A = acid value of glycerol monocaprylate.

www.webofpharma.com

https://thietbiuocngocanh.com/

Calculate the content of mono-, di- and triacylglycerols using the following equations:

$$\text{Monoacylglycerols content} = \frac{X \times (100 - A - B - C)}{100}$$

$$\text{Diacylglycerols content} = \frac{Y \times (100 - A - B - C)}{100}$$

$$\text{Triacylglycerols content} = \frac{Z \times (100 - A - B - C)}{100}$$

A	=	percentage content of free glycerol (see Tests);
B	=	percentage content of water;
X	=	monoacylglycerols content obtained by normalisation;
Y	=	diacylglycerols content obtained by normalisation;
Z	=	triacylglycerols content obtained by normalisation.

LABELLING

The label states the type of glycerol monocaprylate (type I or II).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thietbiuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Monocaprylocaprate

General Notices

(Ph. Eur. monograph 2392)

Ph Eur

DEFINITION

Mixture of monoacylglycerols, mainly mono-*O*-octanoylglycerol and mono-*O*-decanoylglycerol, containing variable quantities of di- and triacylglycerols, obtained by direct esterification of glycerol with caprylic (octanoic) and capric (decanoic) acids, followed by a distillation step in the case of glycerol monocaprylocaprate (type II).

Content

— *glycerol monocaprylocaprate (type I)*:

— *monoacylglycerols*: 45.0 per cent to 75.0 per cent;

— *diacylglycerols*: 20.0 per cent to 50.0 per cent;

— *triacylglycerols*: maximum 10.0 per cent;

— *glycerol monocaprylocaprate (type II)*:

— *monoacylglycerols*: minimum 80.0 per cent;

— *diacylglycerols*: maximum 20.0 per cent;

— *triacylglycerols*: maximum 5.0 per cent.

CHARACTERS

Appearance

Colourless or slightly yellow, oily liquid or soft mass.

Solubility

Practically insoluble in water, very soluble in ethanol (96 per cent) and freely soluble in methylene chloride.

IDENTIFICATION

A. Composition of fatty acids (see Tests).

B. It complies with the limits of the assay (monoacylglycerols).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Acid value (2.5.1)

Maximum 3.0.

Composition of fatty acids (2.4.22, Method C)

Use the mixture of calibrating substances in Table 2.4.22.-2.

Composition of the fatty acid fraction of the substance:

— *caproic acid*: maximum 3.0 per cent;

— *caprylic acid*: 50.0 per cent to 90.0 per cent;

— *capric acid*: 10.0 per cent to 50.0 per cent;

— *lauric acid*: maximum 3.0 per cent;

— *myristic acid*: maximum 1.0 per cent.

Free glycerol

Maximum 3.0 per cent.

Dissolve 1.20 g in 25.0 mL of *methylene chloride R*. Heat to about 50 °C and allow to cool. Add 100 mL of *water R*, shake and add 25.0 mL of *periodic acetic acid solution R*. Shake again and allow to stand for 30 min. Add 40 mL of a 75 g/L solution of *potassium iodide R* and allow to stand for 1 min. Add 1 mL of *starch solution R*. Titrate with *0.1 M sodium thiosulfate* until the aqueous phase becomes colourless. Carry out a blank titration.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 2.3 mg of glycerol.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.00 g.

Total ash (2.4.16)

Maximum 0.5 per cent.

ASSAY

Gas chromatography (2.2.28): use the normalisation procedure.

Test solution To 0.25 g of the substance to be examined, add 5.0 mL of *tetrahydrofuran R* and shake to dissolve.

Reference solution (a) To 0.25 g of *glycerol monocaprylocaprate CRS*, add 5.0 mL of *tetrahydrofuran R* and shake to dissolve.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) To 50 mg of *glycerol 1-octanoate R* and 50 mg of *glycerol 1-decanoate R*, add 2.5 mL of *tetrahydrofuran R* and shake to dissolve.

Column:

— *size*: *l* = 10 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.3 mL/min.

Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 3	60
	3 - 38	60 → 340
	38 - 50	340
Injection port		350
Detector		370

Detection Flame ionisation.

Injection 1 µL.

Identification of peaks Use the chromatogram supplied with *glycerol monocaprylocaprate CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to mono-, di- and triacylglycerols.

System suitability Reference solution (b):

— *resolution*: minimum 5 between the peaks due to glycerol 1-octanoate and glycerol 1-decanoate.

For the calculation of the contents of mono-, di- and triacylglycerols, disregard the peaks with a retention time less than that of the monoacylglycerols, which are due to the impurities of the solvent and to the free fatty acids.

Calculate the percentage content of free fatty acids *(C)* using the following equations:

$$\frac{I_A \times 144}{561.1}$$

I_A = acid value of the glycerol monocaprylocaprate.

www.webofpharma.com

https://thietbiuocngocanh.com/

Calculate the content of mono-, di- and triacylglycerols using the following equations:

$$\text{Monoacylglycerols content} = \frac{X \times (100 - A - B - C)}{X + Y + Z}$$

$$\text{Diacylglycerols content} = \frac{Y \times (100 - A - B - C)}{X + Y + Z}$$

$$\text{Triacylglycerols content} = \frac{Z \times (100 - A - B - C)}{X + Y + Z}$$

A	=	percentage content of free glycerol (see Tests);
B	=	percentage content of water;
X	=	area of the peak due to monoacylglycerols;
Y	=	area of the peak due to diacylglycerols;
Z	=	area of the peak due to triacylglycerols.

LABELLING

The labelling states the type of glycerol monocaprylocaprate (type I or II).

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Monolinoleate

General Notices

(Ph. Eur. monograph 1429)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of monoacylglycerols, mainly mono-oleoyl- and monolinoleoylglycerol, together with variable quantities of di- and triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of linoleic ((9*Z*,12*Z*)-octadeca-9,12-dienoic) acid. A suitable antioxidant may be added.

Content

— *monoacylglycerols*: 32.0 per cent to 52.0 per cent;

— *diacylglycerols*: 40.0 per cent to 55.0 per cent;

— *triacylglycerols*: 5.0 per cent to 20.0 per cent.

CHARACTERS

Appearance

Amber, oily liquid which may be partially solidified at room temperature.

Solubility

Practically insoluble in water, freely soluble in methylene chloride.

IDENTIFICATION

A. Iodine value (see Tests).

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20 mL with the same solvent.

Reference solution Dissolve 1.0 g of *glycerol monolinoleate CRS* in *methylene chloride R* and dilute to 20 mL with the same solvent.

Plate *TLC silica gel plate R*.

www.webofpharma.com

https://thietbiuocngocanh.com/

Mobile phase *hexane R*, *ether R* (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Spray with a 0.1 g/L solution of *rhodamine B R* in *ethanol (96 per cent) R* and examine in ultraviolet light at 365 nm.

Results The spots in the chromatogram obtained with the test solution are similar in position to those in the chromatogram obtained with the reference solution.

C. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*)

Maximum 6.0, determined on 1.0 g.

Iodine value (*2.5.4, Method A*)

100 to 140.

Peroxide value (*2.5.5, Method A*)

Maximum 12.0, determined on 2.0 g.

Saponification value (*2.5.6*)

160 to 180, determined on 2.0 g.

Free glycerol

Maximum 6.0 per cent, determined as described in the assay.

Composition of fatty acids (*2.4.22, Method C*)

Composition of the fatty acid fraction of the substance:

— *palmitic acid*: 4.0 per cent to 20.0 per cent;

— *stearic acid*: maximum 6.0 per cent;

— *oleic acid*: 10.0 per cent to 35.0 per cent;

— *linoleic acid*: minimum 50.0 per cent;

— *linolenic acid*: maximum 2.0 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *arachidic acid*: maximum 1.0 per cent;

— *eicosenoic acid*: maximum 1.0 per cent.

Water (2.5.12)

Maximum 1.0 per cent, determined on 1.00 g. Use as the solvent a mixture of equal volumes of *anhydrous methanol R* and *methylene chloride R*.

Total ash (2.4.16)

Maximum 0.1 per cent.

ASSAY

Size-exclusion chromatography (2.2.30).

Test solution Into a 15 mL flask, weigh about 0.2 g (*m*), to the nearest 0.1 mg. Add 5 mL of *tetrahydrofuran R* and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

Reference solutions Into four 15 mL flasks, respectively weigh, to the nearest 0.1 mg, about 2.5 mg, 5 mg, 10 mg and 20 mg of *glycerol R*. Add 5 mL of *tetrahydrofuran R* and shake until well mixed. Weigh the flasks again and calculate the concentration of glycerol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm,

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

Flow rate 1 mL/min.

Detection Differential refractometer.

Injection 40 µL.

Relative retention With reference to glycerol (retention time = about 15.6 min): triacylglycerols = about 0.76; diacylglycerols = about 0.80; monoacylglycerols = about 0.86.

Calculations:

— *free glycerol*: from the calibration curve obtained with the reference solutions, determine the concentration of glycerol (*C*) in milligrams per gram in the test solution and calculate the percentage content of free glycerol (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

www.webofpharma.com

https://thietbiuocngocanh.com/

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 280}{56.11 \times 10}$$

I_A = acid value (see Tests);

280 = rounded molar mass of linoleic acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole.

— *monoacylglycerols*: calculate the percentage content of monoacylglycerols using the following expression:

$$\left[\frac{X}{X+Y+Z}\ (100 - A - B)\right] - D$$

A = percentage content of free glycerol;

B = percentage content of water (see Tests);

D = percentage content of free fatty acids;

X = area of the peak due to monoacylglycerols and free fatty acids;

Y = area of the peak due to diacylglycerols;

Z = area of the peak due to triacylglycerols.

— *diacylglycerols*: calculate the percentage content of diacylglycerols using the following expression:

$$\frac{Y}{X+Y+Z}\ (100 - A - B)$$

— *triacylglycerols*: calculate the percentage content of triacylglycerols using the following expression:

$$\frac{Z}{X+Y+Z}\ (100 - A - B)$$

STORAGE

In an airtight container, protected from light.

Ph Eur

© Crown Copyright 2022
www.webofpharma.com

https://thietbiuocngocanh.com/

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Monostearate 40-55

General Notices

(Ph. Eur. monograph 0495)

Action and use

Excipient.

Ph Eur

DEFINITION

Mixture of monoacylglycerols, mainly monostearoylglycerol, together with variable quantities of di- and triacylglycerols. It is obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of palmitic (hexadecanoic) or stearic (octadecanoic) acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

Content

— *monoacylglycerols*: 40.0 per cent to 55.0 per cent;

— *diacylglycerols*: 30.0 per cent to 45.0 per cent;

— *triacylglycerols*: 5.0 per cent to 15.0 per cent.

CHARACTERS

Appearance

Hard, waxy mass or unctuous powder or flakes, white or almost white.

Solubility

Practically insoluble in water, soluble in ethanol (96 per cent) at 60 °C.

IDENTIFICATION

First identification: C, D.

Second identification: A, B.

A. Melting point (*2.2.15*): 54 °C to 66 °C.

Introduce the melted substance into the capillary tubes and allow to stand for 24 h in a well-closed container.

www.webofpharma.com

https://thietbiuocngocanh.com/

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.5 g of the substance to be examined in methylene chloride R, with gentle heating, and dilute to 10 mL with the same solvent.

Reference solution Dissolve 0.5 g of glycerol monostearate 40-55 CRS in methylene chloride R, with gentle heating, and dilute to 10 mL with the same solvent.

Plate TLC silica gel plate R.

Mobile phase hexane R, ether R (30:70 *V/V*).

Application 10 µL.

Development Over a path of 15 cm.

Detection Spray with a 0.1 g/L solution of rhodamine B R in ethanol (96 per cent) R and examine in ultraviolet light at 365 nm.

Suitability system Reference solution:

— the chromatogram shows 4 clearly separated spots.

Results The spots in the chromatogram obtained with the test solution are similar in position to those in the chromatogram obtained with the reference solution.

C. Composition of fatty acids (see Tests) according to the type stated on the label.

D. It complies with the limits of the assay (monoacylglycerol content).

TESTS

Acid value (2.5.1)

Maximum 3.0, determined on 1.0 g.

Use a mixture of equal volumes of ethanol (96 per cent) R and toluene R as solvent and heat gently.

Iodine value (2.5.4, Method A)

Maximum 3.0.

Saponification value (2.5.6)

158 to 177, determined on 2.0 g. Carry out the titration with heating.

Free glycerol

Maximum 6.0 per cent, determined as described under Assay.

Composition of fatty acids (2.4.22, Method C)

www.webofpharma.com

https://thietbiuocngocanh.com/

Use the mixture of calibrating substances in Table 2.4.22.-1.

Composition of the fatty-acid fraction of the substance:

Glycerol monostearate 40-55	Composition of fatty acids
Type I	*Stearic acid*: 40.0 per cent to 60.0 per cent *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent
Type II	*Stearic acid*: 60.0 per cent to 80.0 per cent *Sum of the contents of palmitic and stearic acids*: minimum 90.0 per cent
Type III	*Stearic acid*: 80.0 per cent to 99.0 per cent *Sum of the contents of palmitic and stearic acids*: minimum 96.0 per cent

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 1.00 g. Use *pyridine R* as the solvent and heat gently.

Total ash (*2.4.16*)

Maximum 0.1 per cent.

ASSAY

Size-exclusion chromatography (*2.2.30*).

Test solution Into a 15 mL flask, weigh 0.200 g (*m*). Add 5.0 mL of *tetrahydrofuran R* and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (*M*).

Reference solutions Into four 15 mL flasks, respectively weigh 2.5 mg, 5.0 mg, 10.0 mg and 20.0 mg of *glycerol R*, and add 5.0 mL of *tetrahydrofuran R* to each flask. Weigh the flasks again and calculate the concentration of glycerol in milligrams per gram for each reference solution.

Column:

— *size*: *l* = 0.6 m, Ø = 7 mm;

— *stationary phase*: *styrene-divinylbenzene copolymer R* (5 µm) with a pore size of 10 nm.

Mobile phase *tetrahydrofuran R*.

Flow rate 1 mL/min.

Detection Differential refractometer.

Injection 40 µL.

www.webofpharma.com

https://thuocngocanh.com/

Relative retention With reference to glycerol (retention time = about 15 min): triacylglycerols = about 0.75; diacylglycerols = about 0.80; monoacylglycerols = about 0.85.

Calculations:

— *free glycerol*: from the calibration curve obtained with the reference solutions, determine the concentration of glycerol (*C*) in milligrams per gram in the test solution and calculate the percentage content of free glycerol (*A*) in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

— *free fatty acids*: calculate the percentage content of free fatty acids (*D*) using the following expression:

$$\frac{I_A \times 270}{56.11 \times 10}$$

I_A = acid value (see Tests);

270 = average rounded molar mass of stearic acid and palmitic acid, in grams per mole;

56.11 = molar mass of potassium hydroxide, in grams per mole;

— *monoacylglycerols*: calculate the percentage content of monoacylglycerols using the following expression:

$$\left[\frac{X}{X+Y+Z}\ (100 - A - B)\right] - D$$

A = percentage content of free glycerol;

B = percentage content of water (see Tests);

D = percentage content of free fatty acids;

X = area of the peak due to monoacylglycerols and free fatty acids;

Y = area of the peak due to diacylglycerols;

Z = area of the peak due to triacylglycerols;

— *diacylglycerols*: calculate the percentage content of diacylglycerols using the following expression:

$$\frac{Y}{X+Y+Z}\ (100 - A - B)$$

— *triacylglycerols*: calculate the percentage content of triacylglycerols using the following expression:

$$\frac{Z}{X+Y+Z}\ (100 - A - B)$$

LABELLING

The label states the type of glycerol monostearate 40-55.

www.webofpharma.com

https://thuocngocanh.com/

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for glycerol monostearate 40-55 used as matrix former in prolonged-release oral solid dosage forms.

Composition of fatty acids

(see Tests).

Particle-size distribution (*2.9.31* or *2.9.38*)

Powder flow (*2.9.36*)

Thermal analysis (*2.2.34*)

The melting behaviour of the substance as is and after melting followed by solidification when cooling may be considered.

The following characteristics may be relevant for glycerol monostearate 40-55 used as consistency agent in dosage forms for cutaneous application.

Composition of fatty acids

(see Tests).

Thermal analysis (*2.2.34*)

The melting behaviour of the substance as is and after melting followed by solidification when cooling may be considered.

Ph Eur

© Crown Copyright 2022

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycerol Suppositories

General Notices

Glycerin Suppositories

DEFINITION

Gelatin	14 g
Glycerol	70 g
Purified Water	A sufficient quantity

In tropical and subtropical countries the quantity of Gelatin may be increased to an amount not exceeding 18 g.

Extemporaneous preparation

The following directions apply.

Add the Gelatin to about 30 mL of Purified Water heated nearly to boiling, then add the Glycerol previously heated to 100° and heat the mixture on a water bath for 15 minutes or until solution is complete. Adjust the weight of the product to 100 g by the addition of hot Purified Water or by evaporation on a water bath and pour into suitable moulds.

The suppositories comply with the requirements stated under Rectal Preparations and with the following requirements.

Content of glycerol, $C_3H_8O_3$

66.5 to 73.5% w/w.

Disintegration

Maximum time, 1 hour, Appendix XII A2.

ASSAY

Dissolve a number of suppositories containing 8 g of Glycerol in 50 mL of *water* and add sufficient *water* to produce 250 mL. To 5 mL add 150 mL of *water* and 0.25 mL of *bromocresol purple solution* and neutralise with *0.1M sodium hydroxide VS* to the blue colour of the indicator. Add 1.6 g of *sodium periodate* and allow to stand for 15 minutes. Add 3 mL of *propan-1,2-diol*, shake, allow to stand for 5 minutes and titrate with *0.1M sodium hydroxide VS* to the same blue colour. Each mL of *0.1M sodium hydroxide VS* is equivalent to 9.210 mg of $C_3H_8O_3$.

© Crown Copyright 2022

www.webofpharma.com

https://thietbiuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glyceryl Trinitrate Ointment

General Notices

Action and use

Vasodilator.

DEFINITION

Glyceryl Trinitrate Ointment contains Glyceryl Trinitrate in a suitable basis.

The ointment complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements.

Content of glyceryl trinitrate, $C_3H_5N_3O_9$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) To a quantity of the ointment containing 40 mg of Glyceryl Trinitrate add 80 mL of *methanol*, disperse with the aid of ultrasound for 30 minutes, cool in ice and filter. Dilute 1 volume of the filtrate to 5 volumes with *methanol*.

(2) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient *methanol* to produce a solution containing approximately 0.01% w/v of Glyceryl Trinitrate.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel plate* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a current of cool air, spray with freshly prepared *potassium iodide and starch solution*. Expose the plate to *ultraviolet light (254 nm)* for 15 minutes and examine in daylight.

MOBILE PHASE

20 volumes of *ethyl acetate* and 80 volumes of *toluene*.

SYSTEM SUITABILITY

The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the ointment containing 50 mg of Glyceryl Trinitrate add 70 mL of *methanol* and completely disperse with the aid of ultrasound. Cool the contents in ice for 30 minutes, allow to attain room temperature, add sufficient *methanol* to produce 100 mL and centrifuge.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.

(3) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient 1M *hydrochloric acid* to produce a solution containing 0.05% w/v of Glyceryl Trinitrate and heat in a reaction vial at 100° for 30 minutes (production of the dinitrate impurities).

(4) Dilute 1 volume of solution (2) to 10 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for three times the retention time of the principal peak.

MOBILE PHASE

50 volumes of *acetonitrile R1* and 50 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to glyceryl trinitrate (retention time, about 11 minutes) are: glyceryl mononitrate, about 0.23; 1,3-glyceryl dinitrate, about 0.42; 1,2-glyceryl dinitrate, about 0.45.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles the reference chromatogram supplied with *glyceryl trinitrate solution BPCRS,* in that it shows a principal peak due to glyceryl trinitrate and two clearly separated peaks due to the dinitrate impurities.

LIMITS

In the chromatogram obtained with solution (1):

www.webofpharma.com

https://thuocngocanh.com/

the area of any peak due to glyceryl mononitrate, 1,3-glyceryl dinitrate or 1,2-glyceryl dinitrate is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any other *secondary peaks* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the ointment containing 40 mg of Glyceryl Trinitrate add 70 mL of *methanol* and, completely disperse with the aid of ultrasound. Cool the contents in ice for 30 minutes, allow to attain room temperature, add sufficient *methanol* to produce 100 mL and centrifuge.
(2) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient *methanol* to produce a solution containing 0.04% w/v of Glyceryl Trinitrate.
(3) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient 1M *hydrochloric acid* to produce a solution containing 0.05% w/v of Glyceryl Trinitrate and heat in a reaction vial at 100° for 30 minutes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

50 volumes of *methanol* and 50 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to glyceryl trinitrate (retention time, about 9 minutes) are: 1,3-glyceryl dinitrate, about 0.4; 1,2-glyceryl dinitrate, about 0.45; isosorbide dinitrate, about 0.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the peak to valley ratio between 1,3-glyceryl dinitrate and 1,2-glyceryl dinitrate is at least 5.

DETERMINATION OF CONTENT

Calculate the content of $C_3H_5N_3O_9$ in the ointment using the declared content of $C_3H_5N_3O_9$ in *glyceryl trinitrate solution BPCRS*.

www.webofpharma.com

https://thietbiuocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products
Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

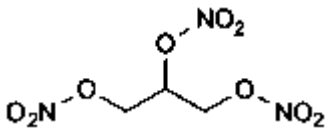
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glyceryl Trinitrate Solution

General Notices

(Ph. Eur. monograph 1331)



$C_3H_5N_3O_9$ 227.1

Action and use

Vasodilator.

Preparations

Glyceryl Trinitrate Ointment

Glyceryl Trinitrate Sublingual Spray

Glyceryl Trinitrate Tablets

Glyceryl Trinitrate Transdermal Patches

When concentrated glyceryl trinitrate solution is demanded, the intention of the purchaser, with respect to the strength expressed, should be ascertained.

Ph Eur

DEFINITION

Ethanolic solution of glyceryl trinitrate containing 1 per cent *m/m* to 10 per cent *m/m* of propane-1,2,3-triyl trinitrate.

Content

96.5 per cent to 102.5 per cent of the declared content of glyceryl trinitrate stated on the label.

CHARACTERS

Appearance

Clear, colourless or slightly yellow solution.

Solubility

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Miscible with acetone and with anhydrous ethanol.

Solubility of pure glyceryl trinitrate: practically insoluble in water, freely soluble in anhydrous ethanol, miscible with acetone.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

Upon diluting glyceryl trinitrate solution, care must be taken to always use anhydrous ethanol, otherwise droplets of pure glyceryl trinitrate may precipitate from the solution.

After examination, the residues and the solutions obtained in both the identification and the test sections must be heated on a water-bath for 5 min with dilute sodium hydroxide solution R.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Place 50 µL of a solution diluted, if necessary, with anhydrous ethanol R, to contain 10 g/L of glyceryl trinitrate, on a disc of potassium bromide R and evaporate the solvent *in vacuo*.

Comparison Ph. Eur. reference spectrum of glyceryl trinitrate.

B. Thin-layer chromatography (2.2.27).

Test solution Dilute a quantity of the substance to be examined corresponding to 50 mg of glyceryl trinitrate to 100 mL with acetone R.

Reference solution Dilute 0.05 mL of glyceryl trinitrate solution CRS to 1 mL with acetone R.

Plate TLC silica gel plate R.

Mobile phase ethyl acetate R, toluene R (20:80 *V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with freshly prepared potassium iodide and starch solution R; expose to ultraviolet light at 254 nm for 15 min and examine in daylight.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. It complies with the limits of the assay.

TESTS

www.webofpharma.com

https://thuocngocanh.com/

Upon diluting glyceryl trinitrate solution, care must be taken to always use anhydrous ethanol, otherwise droplets of pure glyceryl trinitrate may precipitate from the solution.

After examination, the residues and the solutions obtained in both the identification and the test sections must be heated on a water-bath for 5 min with dilute sodium hydroxide solution R.

Appearance of solution

If necessary, dilute the solution to be examined to a concentration of 10 g/L with *anhydrous ethanol R*. The solution is not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Impurity A (inorganic nitrates)

Thin-layer chromatography (*2.2.27*).

Test solution If necessary, dilute the solution to be examined to a concentration of 10 g/L with *anhydrous ethanol R*.

Reference solution Dissolve 5 mg of *potassium nitrate R* in 1 mL of *water R* and dilute to 100 mL with *ethanol (96 per cent) R*.

Plate *TLC silica gel plate R*.

Mobile phase *glacial acetic acid R*, *acetone R*, *toluene R* (15:30:60 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of air until the acetic acid is completely removed.

Detection Spray intensively with freshly prepared *potassium iodide and starch solution R*; expose to ultraviolet light at 254 nm for 15 min and examine in daylight.

Limit:

— *nitrate ion*: any spot due to the nitrate ion in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent of the content of glyceryl trinitrate calculated as potassium nitrate).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dilute a quantity of the substance to be examined equivalent to 5.0 mg of glyceryl trinitrate to 10.0 mL with *water for chromatography R*. *NOTE*: for glyceryl trinitrate solutions of more than 1 per cent *m/m*, dilute first to a 1 per cent solution with *anhydrous ethanol R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water for chromatography R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dilute 25 µL of *glyceryl trinitrate for system suitability CRS* (containing impurities B, C, D and E) to 0.5 mL with *water for chromatography R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 10	90 → 50	10 → 50
10 - 20	50	50

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with *glyceryl trinitrate for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D and E.

Relative retention With reference to glyceryl trinitrate (retention time = about 15.5 min): impurity C = about 0.19; impurity B = about 0.21; impurity E = about 0.63; impurity D = about 0.65.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities C and B; minimum 1.5 between the peaks due to impurities E and D.

Calculation of percentage contents:

— for each impurity, use the concentration of glyceryl trinitrate in reference solution (a).

Limits:

— *impurities B, C, D, E*: for each impurity, maximum 0.5 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.5 per cent;

— *reporting threshold*: 0.05 per cent.

ASSAY

Test solution Prepare a solution containing 1.0 mg of glyceryl trinitrate in 250.0 mL of *methanol R*.

Reference solution Dissolve 70.0 mg of *sodium nitrite R* in *methanol R* and dilute to 250.0 mL with the same solvent. Dilute 5.0 mL of the solution to 500.0 mL with *methanol R*.

Into three 50 mL volumetric flasks introduce 10.0 mL of the test solution, 10.0 mL of the reference solution and 10 mL of *methanol R* as a blank. To each flask add 5 mL of *dilute sodium hydroxide solution R*, close the flask, mix and allow to stand at room temperature for 30 min. Add 10 mL of *sulfanilic acid solution R* and 10 mL of *dilute hydrochloric acid R* and mix. After exactly 4 min, add 10 mL of *naphthylethylenediamine dihydrochloride solution R*, dilute to volume with *water R* and mix. After 10 min read the absorbance (*2.2.25*) of the test solution and the reference solution at 540 nm using the blank solution as the compensation liquid.

Calculate the percentage content of glyceryl trinitrate using the following expression:

$$\frac{A_T \times m_S \times C}{A_R \times m_T \times 60.8}$$

A_T = absorption of the test solution;

m_S = mass of sodium nitrite, in milligrams.

C = percentage content of sodium nitrite used as reference;

A_R = absorption of the reference solution;

m_T = mass of the substance to be examined, in milligrams;

STORAGE

Store the diluted solutions (1 per cent *m/m*) protected from light, at a temperature of 2 °C to 15 °C.

Store the other solutions protected from light, at a temperature of 15 °C to 20 °C.

LABELLING

The label states the declared content of glyceryl trinitrate.

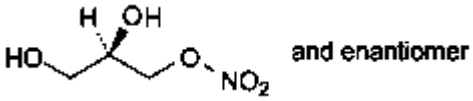
IMPURITIES

Specified impurities *A, B, C, D, E.*

www.webofpharma.com

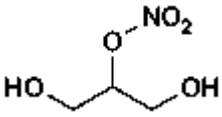
https://thuocngocanh.com/

A. inorganic nitrates,

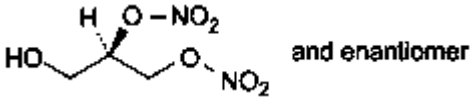


and enantiomer

B. (2*RS*)-2,3-dihydroxypropyl nitrate,

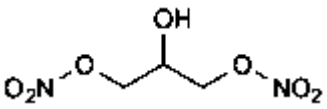


C. 2-hydroxy-1-(hydroxymethyl)ethyl nitrate,



and enantiomer

D. (2*RS*)-3-hydroxypropane-1,2-diyl dinitrate,



E. 2-hydroxypropane-1,3-diyl dinitrate.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glyceryl Trinitrate Sublingual Spray

General Notices

DEFINITION

Glyceryl Trinitrate Sublingual Spray contains Glyceryl Trinitrate Solution in a suitable vehicle either in a suitable pressurised container or in a container fitted with a spray device.

PRODUCTION

A suitable test is carried out to demonstrate the uniformity of dose.

The oromucosal spray complies with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of glyceryl trinitrate, $C_3H_5N_3O_9$

80.0 to 120.0% of the amount stated to be delivered per metered dose.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using a *TLC silica gel plate* (Merck silica gel plates are suitable) and a mixture of 20 volumes of *ethyl acetate* and 80 volumes of *toluene* as the mobile phase. Apply separately to the plate 5 µL of each of the following solutions. For solution (1) expel a number of metered doses containing the equivalent of about 4 mg of glyceryl trinitrate into a beaker, add 5 mL of *acetone*, transfer to a graduated flask and add sufficient *acetone* to produce 10 mL. For solution (2) dilute a quantity of *glyceryl trinitrate solution BPCRS* with *methanol (50%)* to produce a solution containing 0.04% w/v of glyceryl trinitrate. Solution (3) is a mixture of equal volumes of solutions (1) and (2). After removal of the plate, allow it to dry in air and spray with freshly prepared *potassium iodide and starch solution*. Expose the plate to *ultraviolet light (254 nm)* for 15 minutes and examine in daylight. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal spot in the chromatogram obtained with solution (3) appears as a single compact spot.

B. In the Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) expel a number of metered doses containing the equivalent of about 5 mg of glyceryl trinitrate into a beaker, dilute to 5 mL with *methanol*, mix well and add sufficient *water* to produce 10 mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *methanol (50%)*. For solution (3) dilute a

www.webofpharma.com

https://thietbiuocngocanh.com/

quantity of *glyceryl trinitrate solution BPCRS* with sufficient 1M *hydrochloric acid* to produce a solution containing 0.05% w/v of glyceryl trinitrate and heat in a reaction vial at 100° for 30 minutes.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable), (b) as the mobile phase with a flow rate of 1.0 mL per minute a mixture of 50 volumes of *acetonitrile* and 50 volumes of *water* and (c) a detection wavelength of 210 nm.

The test is not valid unless the chromatogram obtained with solution (3) resembles the reference chromatogram supplied with *glyceryl trinitrate solution BPCRS* in that it shows a principal peak due to glyceryl trinitrate and two clearly separated peaks due to the dinitrate impurities with retention times relative to glyceryl trinitrate of approximately 0.5.

In the chromatogram obtained with solution (1) the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%) and the sum of areas of any *secondary peaks* is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (3%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) collect 10 metered doses in a vessel avoiding loss of material, dissolve the expelled material in *methanol* and dilute with sufficient *methanol* to produce a solution containing the equivalent of 0.04% w/v of glyceryl trinitrate. For solution (2) dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient *methanol (50%)* to produce a solution containing 0.04% w/v of glyceryl trinitrate.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable), (b) as the mobile phase with a flow rate of 1.3 mL per minute a mixture of 50 volumes of *methanol* and 50 volumes of *water* and (c) a detection wavelength of 225 nm.

Calculate the content of $C_3H_5N_3O_9$ per metered dose using the declared content of $C_3H_5N_3O_9$ in *glyceryl trinitrate solution BPCRS*.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glyceryl Trinitrate Tablets

General Notices

Glyceryl Trinitrate Sublingual Tablets; Trinitrin Tablets; Nitroglycerin Tablets

DEFINITION

Glyceryl Trinitrate Tablets are *sublingual tablets* made with Mannitol as the basis and may be prepared by adding Glyceryl Trinitrate Solution of an appropriate concentration to dried granules of Mannitol, mixing intimately, drying at a temperature not exceeding 50° or without heating for not more than 4 hours and compressing.

CAUTION Undiluted glyceryl trinitrate can be exploded by percussion or excessive heat. Appropriate precautions should be exercised and only exceedingly small amounts should be isolated.

The tablets comply with the requirements stated under Oromucosal Preparations and with the following requirements.

Content of glyceryl trinitrate, $C_3H_5N_3O_9$

85.0 to 115.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Extract a quantity of the powdered tablets containing 0.5 mg of glyceryl trinitrate with 1 mL of *acetone* and centrifuge.

(2) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient *water* to produce a solution containing 0.05% w/v of glyceryl trinitrate.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.

(b) Use the mobile phase as described below.

(c) Apply 20 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a stream of air, spray with *diphenylamine solution R1* and irradiate for 15 minutes with *ultraviolet light (365 nm)*. Examine the plate in daylight.

MOBILE PHASE

toluene.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

www.webofpharma.com

https://thuocngocanh.com/

B. Extract a quantity of the powdered tablets containing 3 mg of glyceryl trinitrate with 5 mL of *ether* and filter. Evaporate the ether and dissolve the residue in 0.2 mL of *sulfuric acid* containing a trace of *diphenylamine*. An intense blue colour is produced.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing 2.5 mg of glyceryl trinitrate with 10 mL of *acetonitrile* with the aid of ultrasound, filter through a 4-µm filter and dilute one volume of the filtrate with an equal volume of *water*.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient 1M *hydrochloric acid* to produce a solution containing 0.05% w/v of glyceryl trinitrate and heat in a reaction vial at 100° for 30 minutes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for three times the retention time of the principal peak.

MOBILE PHASE

40 volumes of *acetonitrile* and 60 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles the reference chromatogram supplied with *glyceryl trinitrate solution BPCRS* in that it shows a principal peak due to glyceryl trinitrate and two clearly separated peaks due to the dinitrate impurities with retention times relative to glyceryl trinitrate of approximately 0.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any such peaks is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

www.webofpharma.com

https://thietbiuocngocanh.com/

Tablets containing less than 2 mg and/or less than 2% w/w of glyceryl trinitrate comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add 2 mL of *acetonitrile* to one tablet, mix with the aid of ultrasound for 5 minutes, filter through a 4-µm filter and dilute 1 volume of the filtrate with an equal volume of *water*.

(2) Dilute *glyceryl trinitrate solution BPCRS* with the mobile phase to produce a solution containing the equivalent amount of glyceryl trinitrate as that expected for solution (1).

(3) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient 1M *hydrochloric acid* to produce a solution containing 0.05% w/v of glyceryl trinitrate and heat in a reaction vial at 100° for 30 minutes.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used, with the exception of the run time.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) resembles the reference chromatogram supplied with *glyceryl trinitrate solution BPCRS* in that it shows a principal peak due to glyceryl trinitrate and two clearly separated peaks due to the dinitrate impurities with retention times relative to glyceryl trinitrate of approximately 0.5.

DETERMINATION OF CONTENT

Calculate the content of $C_3H_5N_3O_9$ in each tablet from the chromatograms obtained and using the declared content of $C_3H_5N_3O_9$ in *glyceryl trinitrate solution BPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

Glyceryl Trinitrate Tablets should be protected from light and stored in a glass container closed by means of a screw closure lined with aluminium or tin foil; additional packing that absorbs glyceryl trinitrate should be avoided. Glyceryl Trinitrate Tablets should be issued for patients in containers of not more than 100 tablets.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

www.webofpharma.com

https://thietbiuocngocanh.com/
Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap
www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glyceryl Trinitrate Transdermal Patches

General Notices

DEFINITION

Glyceryl Trinitrate Transdermal Patches contain glyceryl trinitrate in a suitable matrix or reservoir presentation. They are prepared from Glyceryl Trinitrate Solution.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of glyceryl trinitrate.

The transdermal patches comply with the requirements stated under Transdermal Patches and with the following requirements.

Content of glyceryl trinitrate, $C_3H_5N_3O_9$

90.0 to 115.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Clean the outer surface of a patch using a lint-free cloth moistened with *methanol*. Remove the release liner and score the exposed surface. Place the patch in a flask containing sufficient *methanol* to produce a solution containing 0.1% w/v of glyceryl trinitrate, mix with the aid of ultrasound in a water bath at 40° for 15 minutes and then shake mechanically at room temperature for 3 hours. Dilute the methanolic extract with sufficient *water* to produce a final concentration of 0.05% w/v of glyceryl trinitrate.

(2) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with *methanol (50%)* to produce a solution containing 0.05% w/v of glyceryl trinitrate.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with freshly prepared *potassium iodide and starch solution*. Expose the plate to *ultraviolet light (254 nm)* for 15 minutes and examine in daylight.

MOBILE PHASE

20 volumes of *ethyl acetate* and 80 volumes of *toluene*.

CONFIRMATION

www.webofpharma.com

https://thuocngocanh.com/

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the test for Uniformity of content, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Clean the outer surface of five patches using a lint-free cloth moistened with *methanol*. Remove the release liners and score the exposed surfaces. Place the patches in a flask containing sufficient *methanol* to produce a solution containing 0.1% w/v of glyceryl trinitrate, mix with the aid of ultrasound in a water bath at 40° for 15 minutes and then shake mechanically at room temperature for 3 hours. Dilute the methanolic extract with sufficient *water* to produce a final concentration of 0.05% w/v of glyceryl trinitrate.

(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol (50%)*.

(3) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient 1M *hydrochloric acid* to produce a solution containing 0.05% w/v of glyceryl trinitrate and heat in a reaction vial at 100° for 30 minutes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 210 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

Equal volumes of *acetonitrile* and *water*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) closely resembles the reference chromatogram supplied with *glyceryl trinitrate solution BPCRS* in that it shows a principal peak due to glyceryl trinitrate and two clearly separated peaks due to the dinitrate impurities with retention times relative to glyceryl trinitrate of approximately 0.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks* is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (3%).

www.webofpharma.com

https://thuocngocanh.com/

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Comply with the requirements stated under *uniformity of content*, Appendix XII C3, Test C, with respect to the individual content of each dosage unit and using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Clean the outer surface of a patch using a lint-free cloth moistened with *methanol*. Remove the release liner and score the exposed surface. Place the patch in a flask containing sufficient *methanol* to produce a solution containing 0.1% w/v of glyceryl trinitrate, mix with the aid of ultrasound in a water bath at 40° for 15 minutes, shake mechanically at room temperature and dilute a volume of the solution with an equal volume of *water*.

(2) Dilute a quantity of *glyceryl trinitrate solution BPCRS* with sufficient *methanol (50%)* to produce a solution containing 0.05% w/v of glyceryl trinitrate.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_3H_5N_3O_9$ in the transdermal patch using the declared content of $C_3H_5N_3O_9$ in *glyceryl trinitrate solution BPCRS*.

ASSAY

Use the average of the 10 results obtained in the test for Uniformity of content.

IMPURITIES

A. Glyceryl-1,2-dinitrate,

B. Glyceryl-1,3-dinitrate.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycine

General Notices

(Ph. Eur. monograph 0614)

$C_2H_5NO_2$ 75.1 *56-40-6*

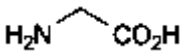
Action and use

Amino acid used for bladder irrigation during surgery.

Preparation

Glycine Irrigation Solution

Ph Eur



DEFINITION

2-Aminoacetic acid.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, very slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

www.webofpharma.com

https://thuocngocanh.com/

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *glycine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol (60 per cent V/V) R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 10 mg of *glycine CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Plate *cellulose for chromatography R* as the coating substance.

Mobile phase *glacial acetic acid R*, *water R*, *butanol R* (20:20:60 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying At 80 °C for 30 min.

Detection Spray with *ninhydrin solution R* and heat at 105 °C for 15 min.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. Dissolve 50 mg in 5 mL of *water R*, add 1 mL of *strong sodium hypochlorite solution R* and boil for 2 min. Add 1 mL of *hydrochloric acid R* and boil for 4-5 min. Add 2 mL of *hydrochloric acid R* and 1 mL of a 20 g/L solution of *resorcinol R*, boil for 1 min and cool. Add 10 mL of *water R* and mix. To 5 mL of the solution add 6 mL of *dilute sodium hydroxide solution R*. The solution is violet with greenish-yellow fluorescence. After a few minutes, the colour becomes orange and then yellow and an intense fluorescence remains.

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (2.2.3)

5.9 to 6.4.

www.webofpharma.com

https://thuocngocanh.com/

Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture To 500 mL of the mobile phase add 1.5 mL of *phosphoric acid R*.

Test solution Dissolve 0.200 g of the substance to be examined in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 80 mg of *iminodiacetic acid R* (impurity A) and 80 mg of the substance to be examined in the solvent mixture and dilute to 50 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of *glycine anhydride R* (impurity B), 50.0 mg of *diglycine R* (impurity H) and 50.0 mg of *triglycine R* (impurity I) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R1* (5 µm);

— *temperature*: 25 °C.

Mobile phase Dissolve 1.4 g of *sodium pentanesulfonate R* in 900 mL of *water for chromatography R*, adjust to pH 2.2 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 10 µL.

Run time 4 times the retention time of glycine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, H and I.

Relative retention With reference to glycine (retention time = about 5.5 min): impurity A = about 0.7; impurity B = about 0.75; impurity H = about 1.7; impurity I = about 2.0.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurity A and glycine.

Calculation of percentage contents:

www.webofpharma.com

https://thuocngocanh.com/

— for each impurity, use the concentration of glycine in reference solution (a);

— for impurities B, H and I, use the concentration of the corresponding impurity in reference solution (c).

Limits:

— *impurities B, H, I*: for each impurity, maximum 0.10 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Ninhydrin-positive substances

Amino acid analysis (2.2.56). For analysis, use Method 1.

The concentrations of the test solution and the reference solutions may be adapted according to the sensitivity of the equipment used. The concentrations of all solutions are adjusted so that the system suitability requirements described in general chapter 2.2.46 are fulfilled, keeping the ratios of concentrations between all solutions as described.

Solution A water R or a sample preparation buffer suitable for the apparatus used.

Test solution Dissolve 30.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Dissolve 30.0 mg of proline R in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of the solution to 250.0 mL with solution A.

Reference solution (c) Dilute 6.0 mL of ammonium standard solution (100 ppm NH_4) R to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with solution A.

Reference solution (d) Dissolve 30 mg of isoleucine R and 30 mg of leucine R in solution A and dilute to 50.0 mL with solution A. Dilute 1.0 mL of the solution to 200.0 mL with solution A.

Blank solution Solution A.

Inject suitable, equal amounts of the test, blank and reference solutions (a), (b) and (d) into the amino acid analyser. Run a program suitable for the determination of physiological amino acids.

System suitability Reference solution (d):

— resolution: minimum 1.5 between the peaks due to isoleucine and leucine.

Calculation of percentage contents:

www.webofpharma.com

https://thuocngocanh.com/

— for any ninhydrin-positive substance detected at 570 nm, use the concentration of glycine in reference solution (a);

— for any ninhydrin-positive substance detected at 440 nm, use the concentration of proline in reference solution (b); if a peak is above the reporting threshold at both wavelengths, use the result obtained at 570 nm for quantification.

Limits:

— *any ninhydrin-positive substance*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Chlorides (2.4.4)

Maximum 75 ppm.

Dissolve 0.67 g in *water R* and dilute to 15 mL with the same solvent.

Ammonium

Amino acid analysis (2.2.56) as described in the test for ninhydrin-positive substances with the following modifications.

Injection Test solution, reference solution (c) and blank solution.

Limit:

— *ammonium at 570 nm*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.02 per cent), taking into account the peak due to ammonium in the chromatogram obtained with the blank solution.

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 70.0 mg in 5 mL of *anhydrous formic acid R*. Add 50 mL of *anhydrous acetic acid R*. Immediately after dissolution, titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.2.20).

1 mL of *0.1 M perchloric acid* is equivalent to 7.51 mg of $C_2H_5NO_2$.

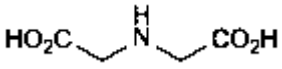
IMPURITIES

Specified impurities *B, H, I.*

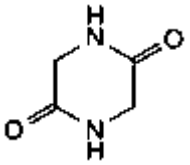
www.webofpharma.com

https://thuocngocanh.com/

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, D, E, F, G.*

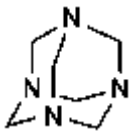


A. 2,2′-iminodiacetic acid,



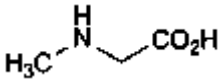
B. piperazine-2,5-dione (glycine anhydride),

C. 2-chloroacetic acid,

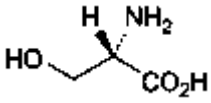


D. 1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane,

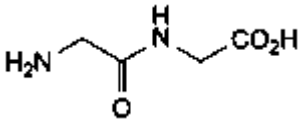
E. 3-aminopropanoic acid (β-alanine),



F. 2-(methylamino)acetic acid (sarcosine),



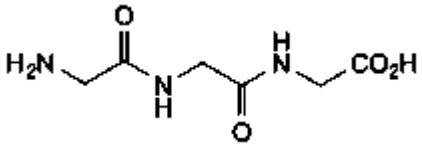
G. (2*S*)-2-amino-3-hydroxypropanoic acid (serine),



www.webofpharma.com

https://thuocngocanh.com/

H. 2-[(2-aminoacetyl)amino]acetic acid (diglycine),



I. 2-[[2-[(2-aminoacetyl)amino]acetyl]amino]acetic acid (triglycine).

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycine Irrigation Solution

General Notices

DEFINITION

Glycine Irrigation Solution is a sterile solution of Glycine in Water for Irrigation.

The irrigation solution complies with the requirements stated under Preparations for Irrigation and with the following requirements.

Content of glycine, $C_2H_5NO_2$

95.0 to 105.0% of the stated amount.

CHARACTERISTICS

A colourless solution.

IDENTIFICATION

A. Evaporate 5 mL to dryness on a water bath and dry at 105° for 1 hour. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of glycine *(RS 171)*.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute the irrigation solution with *water* to contain 0.25% w/v of Glycine.

(2) 0.25% w/v of *glycine* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* GF_{254}.

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry it at 100° to 105° for 10 minutes, spray with *ninhydrin solution* and heat at 100° to 105° for 2 minutes.

MOBILE PHASE

30 volumes of 13.5M *ammonia* and 70 volumes of *propan-1-ol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

TESTS

www.webofpharma.com

https://thietbiluocngocanh.com/

Acidity

pH, 4.5 to 6.5, Appendix V L.

Ammonium compounds

Dilute a volume containing 0.2 g of Glycine to 70 mL with *water* in an ammonia-distillation apparatus, add 25 mL of a solution prepared by boiling 25 mL of 5M *sodium hydroxide* with 50 mL of *water* and 50 mg of *aluminium* until the volume is reduced to 25 mL and distil into 2 mL of a saturated solution of *boric acid* until 50 mL is obtained. Add 2 mL of a solution prepared by boiling 25 mL of 5M *sodium hydroxide* with 50 mL of *water* until the volume is reduced to 25 mL and 2 mL of *alkaline potassium tetraiodomercurate solution*. Any colour produced is not more intense than that obtained by treating 70 mL of *water* containing 4 mL of *ammonia* *standard solution (10 ppm NH_4)* in the same manner, beginning at the words 'add 25 mL of…' (200 ppm, calculated with reference to the content of glycine).

ASSAY

Dilute a volume containing 0.15 g of Glycine to 25 mL with *water* and add 10 mL of *formaldehyde solution* previously adjusted to pH 9.0 and 0.25 mL of a mixed indicator solution prepared by dissolving 75 mg of *phenolphthalein* and 25 mg of *thymol blue* in 100 mL of *ethanol (50%)*. Titrate with *0.1M sodium hydroxide VS* until the yellow colour disappears and a faint violet colour is produced. Each mL of *0.1M sodium hydroxide VS* is equivalent to 7.507 mg of $C_2H_5NO_2$.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycopyrronium Bromide Cream

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Anticholinergic; used in the treatment of hyperhidrosis.

DEFINITION

Glycopyrronium Bromide Cream contains Glycopyrronium Bromide in a suitable basis.

The cream complies with the requirements stated under Topical Semi-solid Preparations and with the following requirements. Where appropriate, the cream also complies with the requirements stated under Unlicensed Medicines.

Content of glycopyrronium bromide, $C_{19}H_{28}BrNO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Place a quantity of the cream containing 5 mg of Glycopyrronium Bromide into a ground-glass-stoppered centrifuge tube, add 50 mL of *water*, heat at 60° for 15 minutes and allow to cool. Shake the cooled solution for 15 minutes and then centrifuge at 3000 rpm for 15 minutes. Carefully remove the lower layer using a pipette and filter using a 0.45-µm PTFE syringe filter.

(2) 0.01% w/v of *glycopyrronium bromide BPCRS* in *water*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 30 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a solution containing 10 volumes of *potassium iodide solution*, 10 volumes of *potassium iodobismuthate solution*, 12 volumes of *glacial acetic acid* and 67 volumes of *water*.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *water* and 60 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless the chromatogram obtained with solution (3) appears as a single, compact spot.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Place a quantity of the cream containing 5 mg of Glycopyrronium Bromide into a ground-glass-stoppered centrifuge tube, add 20 mL of mobile phase A, heat at 60° for 10 minutes and allow to cool. Mix the cooled solution using a vortex mixer for 1 minute and then centrifuge at 3000 rpm for 15 minutes. Carefully remove the lower layer using a pipette and filter using a 0.45-µm PTFE syringe filter.
(2) Dilute 1 volume of solution (1) to 100 volumes; further dilute 1 volume to 10 volumes.
(3) 0.05% w/v of *glycopyrronium for peak identification EPCRS* (contains impurities E and I).
(4) Dilute a mixture containing 1 volume of a 0.1% w/v solution of *benzaldehyde* (impurity F) and 2 volumes of a 0.05% w/v solution of *glycopyrronium bromide BPCRS* to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Inertsil ODS-3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 0.25 g of *sodium heptanesulfonate* in 615 mL of a 0.163% w/v solution of *anhydrous sodium sulfate*; add 3 mL of a 0.515% w/v solution of *sulfuric acid*, 150 mL of *methanol R2* and 235 mL of *acetonitrile R1*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-30	100 → 50	0 → 50	linear gradient
30-45	50	50	isocratic

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
45-47	50 → 100	50 → 0	linear gradient
47-55	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to glycopyrronium (retention time about 11 minutes) are: impurity E, about 0.7; impurity F (benzaldehyde), about 0.8; impurity I, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity F and glycopyrronium is at least 5.0.

LIMITS

Use the chromatogram obtained with solution (3) and the chromatogram supplied with *glycopyrronium for peak identification EPCRS* to identify the peaks due to impurities E and I.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity I is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%) and any peak due to bromide.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A as described under Related substances.

(1) Place a weighed quantity of the cream containing 2 mg of Glycopyrronium Bromide into a ground-glass-stoppered centrifuge tube, add 20 mL of mobile phase A, heat at 60° for 10 minutes and allow to cool. Mix the cooled solution using a vortex mixer for 1 minute and then centrifuge at 3000 rpm for 15 minutes. Carefully remove the lower layer using a pipette and filter using a 0.45-µm PTFE syringe filter.
(2) 0.01% w/v of *glycopyrronium bromide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but using isocratic elution and mobile phase A.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The Assay is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is between 0.8 and 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{28}BrNO_3$ in the cream using the declared content of $C_{19}H_{28}BrNO_3$ in *glycopyrronium bromide BPCRS*.

IMPURITIES

With the exception of impurity N, the impurities limited by the requirements of this monograph include those listed under Glycopyrronium Bromide.

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Glycopyrronium Bromide Solution

General Notices

Glycopyrronium Bromide Cutaneous Solution

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Anticholinergic; used in the treatment of hyperhidrosis.

DEFINITION

Glycopyrronium Bromide Solution is a *cutaneous solution*. It contains Glycopyrronium Bromide in a suitable aqueous vehicle.

The solution complies with the requirements stated under Liquids for Cutaneous Application and with the following requirements. Where appropriate, the solution also complies with the requirements stated under Unlicensed Medicines.

Content of glycopyrronium bromide, $C_{19}H_{28}BrNO_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions in *water*.

(1) Dilute a volume of the solution, if necessary, to produce a solution containing 0.01% w/v of Glycopyrronium Bromide.

(2) 0.01% w/v of *glycopyrronium bromide BPCRS*.

(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 30 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in air, spray with a solution containing 10 volumes of *potassium iodide solution*, 10 volumes of *potassium iodobismuthate solution*, 12 volumes of *glacial acetic acid* and 67 volumes of *water*.

MOBILE PHASE

20 volumes of *glacial acetic acid*, 20 volumes of *water* and 60 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) appears as a single, compact spot.

www.webofpharma.com

https://thuocngocanh.com/

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A.

(1) Dilute a quantity of the solution, if necessary, to contain 0.05% w/v of Glycopyrronium Bromide and filter (a PTFE syringe filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes; further dilute 1 volume to 10 volumes.
(3) 0.05% w/v of *glycopyrronium for peak identification EPCRS* (contains impurities E and I).
(4) Dilute a mixture containing 1 volume of a 0.1% w/v solution of *benzaldehyde* (impurity F) and 2 volumes of a 0.05% w/v solution of *glycopyrronium bromide BPCRS* to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (3 µm) (Inertsil ODS-3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Dissolve 0.25 g of *sodium heptanesulfonate* in 615 mL of a 0.163% w/v solution of *anhydrous sodium sulfate*; add 3 mL of a 0.515% w/v solution of *sulfuric acid*, 150 mL of *methanol R2* and 235 mL of *acetonitrile R1*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-30	100 → 50	0 → 50	linear gradient
30-45	50	50	isocratic
45-47	50 → 100	50 → 0	linear gradient

www.webofpharma.com

https://thuocngocanh.com/

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
47-55	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to glycopyrronium (retention time about 11 minutes) are: impurity E, about 0.7; impurity F (benzaldehyde), about 0.8; impurity I, about 2.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity F and glycopyrronium is at least 5.0.

LIMITS

Use the chromatogram obtained with solution (3) and the chromatogram supplied with *glycopyrronium for peak identification EPCRS* to identify the peaks due to impurities E and I.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity I is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity E is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%) and any peak due to bromide.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase A as described under Related substances.

(1) Dilute a quantity of the solution to contain 0.01% w/v of Glycopyrronium Bromide and filter (a PTFE syringe filter is suitable).
(2) 0.01% w/v of *glycopyrronium bromide BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but using isocratic elution and mobile phase A.

SYSTEM SUITABILITY

The Assay is not valid unless the *symmetry factor* of the principal peak in the chromatogram obtained with solution (2) is between 0.8 and 2.0.

www.webofpharma.com

https://thuocngocanh.com/

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{28}BrNO_3$ in the solution using the declared content of $C_{19}H_{28}BrNO_3$ in *glycopyrronium bromide BPCRS*.

IMPURITIES

With the exception of impurity N, the impurities limited by the requirements of this monograph include those listed under Glycopyrronium Bromide.

© Crown Copyright 2022

www.webofpharma.com

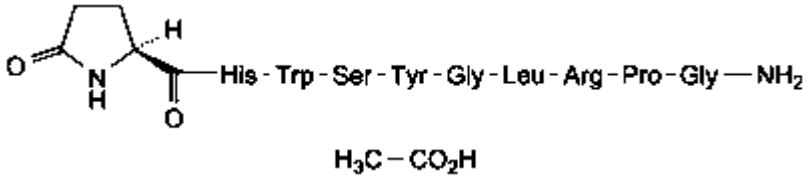
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Gonadorelin Acetate

General Notices

(Ph. Eur. monograph 0827)



$C_{57}H_{79}N_{17}O_{15}$ 1242 *499785-55-6*

Action and use

Gonadotropin-releasing hormone; treatment of prostate cancer.

Ph Eur

DEFINITION

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosylglycyl-L-leucyl-L-arginyl-L-prolylglycinamide acetate.

Acetate form of a synthetic hypothalamic peptide that stimulates the release of follicle-stimulating hormone and luteinising hormone from the pituitary gland.

Content

95.0 per cent to 102.0 per cent of the peptide $C_{55}H_{75}N_{17}O_{13}$ (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance

White or slightly yellowish powder, hygroscopic.

Solubility

Soluble in water, sparingly soluble in methanol. It dissolves in a 1 per cent *V/V* solution of glacial acetic acid.

IDENTIFICATION

Carry out either tests A, B or tests A, C.

www.webofpharma.com

https://thuocngocanh.com/

A. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

B. Nuclear magnetic resonance spectrometry (*2.2.64*).

Preparation 4 mg/mL solution in a mixture of 20 volumes of *deuterated acetic acid R* and 80 volumes of *deuterium oxide R*.

Comparison Dissolve the contents of a vial of *gonadorelin for NMR identification CRS* in a mixture of 20 volumes of *deuterated acetic acid R* and 80 volumes of *deuterium oxide R* to obtain a concentration of 4 mg/mL.

Operating conditions:

— *field strength*: minimum 300 MHz;

— *temperature*: 27 °C.

Results Examine the ^{1}H NMR spectrum from 0 ppm to 9 ppm. The ^{1}H NMR spectrum obtained is qualitatively similar to the ^{1}H NMR spectrum obtained with *gonadorelin for NMR identification CRS*.

C. Amino acid analysis (*2.2.56*). Method 1 for hydrolysis and method 1 for analysis are suitable.
Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids, taking 1/8 of the sum of the number of moles of histidine, glutamic acid, leucine, proline, glycine, tyrosine and arginine as equal to 1. The values fall within the following limits: serine and tyrosine 0.7 to 1.05; glutamic acid, proline, leucine, histidine and arginine 0.9 to 1.1; glycine 1.8 to 2.2. Lysine and isoleucine are absent, and not more than traces of other amino acids are present.

TESTS

Specific optical rotation (*2.2.7*)

-65 to -58 (anhydrous and acetic acid-free substance).

Dissolve 10.0 mg in 1.0 mL of a 1 per cent *V/V* solution of *glacial acetic acid R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve the substance to be examined in *water R* to obtain a concentration of 1.0 mg/mL.

Reference solution (a) Dissolve the contents of a vial of *gonadorelin CRS* in *water R* to obtain a concentration of 1.0 mg/mL.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (c) Dissolve the contents of a vial of *gonadorelin for system suitability A CRS* (containing impurities C, E, F and G) in 1.0 mL of *water R*.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 13 volumes of *acetonitrile R1* and 87 volumes of a 1.18 per cent *V/V* solution of *phosphoric acid R* previously adjusted to pH 2.3 with *triethylamine R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Run time Twice the retention time of gonadorelin.

Relative retention With reference to gonadorelin (retention time = about 12-16 min): impurity C = about 0.7; impurity E = about 0.8; impurities F and G = about 1.2.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities C and E.

Limits:

— *impurity E*: maximum 2.0 per cent;

— *sum of impurities F and G*: maximum 1.5 per cent;

— *impurity C*: maximum 1.0 per cent;

— *unspecified impurities*: for each impurity, maximum 0.5 per cent;

— *total*: maximum 5.0 per cent;

— *reporting threshold*: 0.1 per cent.

Acetic acid (*2.5.34*)

4.0 per cent to 7.5 per cent.

Test solution Dissolve 10.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 mL with the same mixture of solvents.

Water (*2.5.32*)

Maximum 7.0 per cent, determined on 20.0 mg.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

www.webofpharma.com

https://thuocngocanh.com/

Injection Test solution and reference solution (a).

Calculate the percentage content of gonadorelin ($C_{55}H_{75}N_{17}O_{13}$) taking into account the assigned content of $C_{55}H_{75}N_{17}O_{13}$ in *gonadorelin CRS*.

STORAGE

In an airtight container, protected from light at a temperature of 2 °C to 8 °C. If the substance is sterile, the container is also sterile and tamper-evident.

LABELLING

The label states:

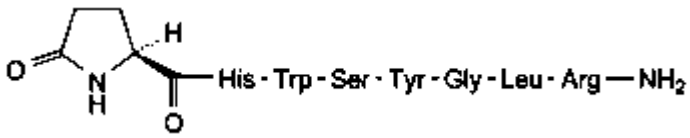
— the gonadorelin peptide content;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

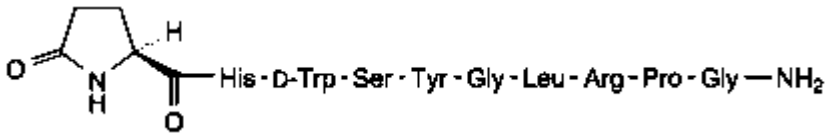
IMPURITIES

Specified impurities *C, E, F, G.*

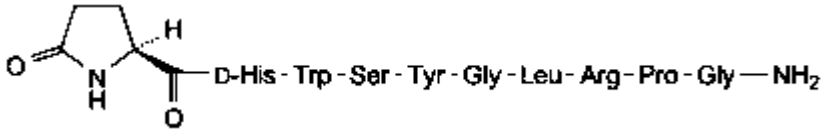
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D.*



C. des-9-L-proline,10-L-glycine-gonadorelin,



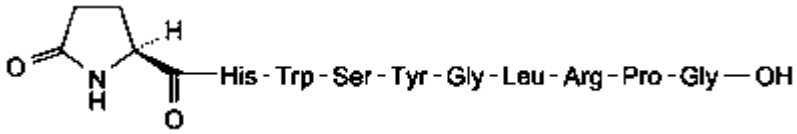
D. [3-D-tryptophan]gonadorelin,



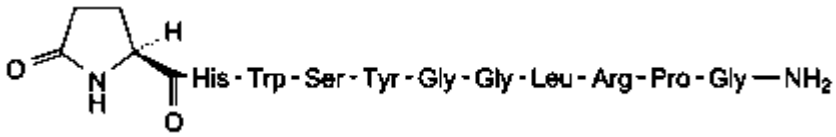
E. [2-D-histidine]gonadorelin,

www.webofpharma.com

https://thuocngocanh.com/



F. [10-glycine]gonadorelin,



G. endo-5a-glycine-gonadorelin.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Goserelin Implants

General Notices

Action and use

Gonadotrophin-releasing hormone, gonadorelin analogue; treatment of prostate cancer.

DEFINITION

Goserelin Implants are biodegradable and biocompatible cylinders for subcutaneous injection containing Goserelin, as acetate, dispersed in a polymeric matrix. They are formulated so that the medicament is released over a period of weeks.

The implants comply with the requirements stated under Parenteral Preparations and with the following requirements.

Content of goserelin, $C_{59}H_{84}N_{18}O_{14}$

90.0 to 110.0% of the stated amount of the peptide.

IDENTIFICATION

A. In the test for Uniformity of content, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Drug release

NOTE: *Suitable procedures should be employed to minimise the presence of bacteria on glassware immediately prior to the dissolution tests*.

For 3.6 mg implants

PROCEDURE

Perform the test in a 120-mL flat-bottomed glass jar with a cap, incubated at 39°± 0.5°. Use as the medium 50 mL of a pH 7.4 buffer solution prepared by dissolving 25.8 g of *anhydrous disodium hydrogen orthophosphate*, 1.92 g of *citric acid* and 0.2 g of *sodium azide* in sufficient *distilled water* to produce 1000 mL. Adjust the pH of the resulting solution to 7.4 with *anhydrous disodium hydrogen orthophosphate* or *citric acid*, if necessary, and filter through a sterile filter with a nominal pore size not greater than 0.2 µm into a sterile container. Place 5 implants into the glass vessel, add 50 mL of the medium and place in the incubator. At the times specified in Table I remove the vessel from the incubator and allow to cool to room temperature. Swirl gently to ensure a uniform solution and withdraw a 5-mL sample. Dilute the sample with 5 mL of the medium, filter if necessary and measure the average of the individual *absorbance* values obtained at 1 nm intervals between 275 nm and 285 nm, Appendix II B, using the dissolution medium in the reference cell. Add 5 mL of the

www.webofpharma.com

https://thuocngocanh.com/

medium to the dissolution vessel to replace the volume removed and return the vessel to the incubator. At least three replicate analyses should be performed.

Table I

Test Duration Hours (days)	Amount dissolved (each replicate)
168 (7)	2 to 20%
336 (14)	25 to 55%
408 (17)	35 to 75%
504 (21)	65 to 90%
672 (28)	85 to 105%

DETERMINATION OF CONTENT

Calculate the content of $C_{59}H_{84}N_{18}O_{14}$ dissolved in the portions of the medium from the *absorbance* obtained from a solution prepared by diluting a suitable amount of *goserelin EPCRS* in the dissolution medium and using the declared content of $C_{59}H_{84}N_{18}O_{14}$ in *goserelin EPCRS*; at the times specified in Table I the cumulative percentages comply with the criteria given.

For 10.8 mg implants

PROCEDURE

Perform the test using the same apparatus as described for the 3.6 mg strength implant. Use as the medium 50 mL of a phosphate buffered saline pH 7.4 (PBS) solution prepared by mixing 8 g of *sodium chloride*, 0.19 g of *potassium dihydrogen orthophosphate*, 1.38 g of *anhydrous disodium hydrogen orthophosphate* and 0.2 g of *sodium azide* in 1000 mL of *distilled water*. Adjust the pH of the solution, if necessary, to 7.4 with *2M hydrochloric acid*. Filter the solution through a sterile filter with a nominal pore size not greater than 0.2 µm into a sterile container. Transfer 50 mL of medium to a vessel and heat at 39°± 0.5°. Place a single implant into the vessel and withdraw 5-mL aliquots at 24, 72, 168 and 264 hours (1, 3, 7 and 11 days) and 20-mL aliquots at 336, 504, 672, 840, 1008, 1176, 1344, 1512, 1680, 1848 and 2016 hours (14, 21, 28, 35, 42, 49, 56, 63, 70, 77 and 84 days) following gentle swirling to ensure a uniform solution. Replace the volume removed with the equivalent amount of warmed medium. Filter the aliquot, if necessary, and measure the average of the individual absorbance values obtained at 1 nm intervals between 275 nm and 285 nm, Appendix II B, using the dissolution medium in the reference cell. At least six replicate analyses should be performed.

www.webofpharma.com

https://thuocngocanh.com/

Table II

Test Duration Hours (days)	Amount dissolved (each replicate)
72 (3)	5 to 30%
336 (14)	10 to 45%
840 (35)	15 to 60%
1,344 (56)	55 to 90%
2,016 (84)	Not less than 70%

DETERMINATION OF CONTENT

Calculate the content of $C_{59}H_{84}N_{18}O_{14}$ dissolved in the portions of the medium from the *absorbance* obtained from a solution prepared by diluting a suitable amount of *goserelin EPCRS* in the dissolution medium and using the declared content of $C_{59}H_{84}N_{18}O_{14}$ in *goserelin EPCRS*. At all time points calculate the cumulative percentage of the labelled amount of $C_{59}H_{84}N_{18}O_{14}$ dissolved; at the times specified in Table II the cumulative percentages comply with the criteria given.

Related substances

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Weigh and dissolve 10 implants, with the aid of ultrasound, in a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile* to obtain a solution containing 0.2% w/v of Goserelin.

(2) Dilute 1 volume of solution (1) to 100 volumes using a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile*.

(3) Dilute 1 volume of solution (2) to 10 volumes using a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile*.

(4) 0.002% w/v each of *4-D-Ser-goserelin EPCRS* and *goserelin EPCRS* in water.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.8 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 220 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

0.272% w/v of *potassium dihydrogen orthophosphate* in a mixture of 27 volumes of *acetonitrile* and 73 volumes of *water*. Adjust the pH to 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to goserelin (retention time about 30 minutes) of 4-D-Ser-goserelin is about 0.84.

www.webofpharma.com

https://thuocngocanh.com/

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution* between the peaks due to 4-D-Ser-goserelin and goserelin is at least 4.5;

the *symmetry factor* of the peak due to goserelin is less than 2.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks* is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (4%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.1%).

B. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions.

(1) Weigh and dissolve 10 implants, with the aid of ultrasound, in a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile* to obtain a solution containing 0.2% w/v of Goserelin.

(2) Dilute 1 volume of solution (1) to 100 volumes using a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile*.

(3) Dilute 1 volume of solution (2) to 20 volumes using a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile*.

(4) 0.002% w/v each of *4-D-Ser-goserelin EPCRS* and *goserelin EPCRS* in a mixture of 20 volumes of water and 80 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 7.8 mm) packed with *hydrophilic silica gel for chromatography* (5 µm) with a fractionation range for proteins with a relative molecular mass of approximately 4000 to 500 000 (TSK-GEL-G2000 SWXL is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 5 µL of each solution.

MOBILE PHASE

8 volumes of a solution prepared as described below and 92 volumes of *acetonitrile*.

To prepare the solution add 167.5 g of a 60% w/v solution of *perchloric acid* to a 1000-mL volumetric flask, cool in ice and dilute to volume with 1M *sodium hydroxide*. To 100 mL of this solution add sufficient *water* to produce 1000 mL and adjust the pH of the solution to 2.1 with 5 M *sodium hydroxide*.

When the chromatograms are recorded using the prescribed conditions the retention times relative to goserelin (retention time about 40 minutes) are: impurity 11, about 0.93; impurity 7 (polymer envelope), about 0.1 to 0.6.

SYSTEM SUITABILITY

www.webofpharma.com

https://thuocngocanh.com/

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to 4-D-Ser-goserelin and goserelin is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 11 is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%);

the sum of the areas of any peaks corresponding to the polymer envelope is not greater than 5.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5.5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.05%).

C. Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions.

(1) Weigh and dissolve 10 implants, with the aid of ultrasound, in a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile* to obtain a solution containing 0.2% w/v of Goserelin.

(2) Dilute 1 volume of solution (1) to 100 volumes using a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile*.

(3) To 4 mg of *goserelin EPCRS* add 250 µL of *trifluoroacetic acid* and leave to stand for 24 hours. Dissolve the product in 20 mL of a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile* to obtain a solution containing des-*t*-butyl-goserelin.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 7.8 mm) packed with *hydrophilic silica gel for chromatography* (5 µm) with a fractionation range for proteins with a relative molecular mass of approximately 4000 to 500 000 (TSK-GEL-G2000 SWXL is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 280 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

12.5 volumes of a solution prepared as described below and 87.5 volumes of *acetonitrile*.

Add 167.5 g of a 60% w/v solution of *perchloric acid* to a 1000-mL volumetric flask, cool in ice and dilute to volume with 1M *sodium hydroxide*. To 100 mL of this solution add sufficient *water* to produce 1000 mL and adjust the pH of the solution to 2.1 with 5M *sodium hydroxide*.

When the chromatograms are recorded under the prescribed conditions the retention time relative to des-*t*-butyl-goserelin (retention time about 20 minutes) of impurity 13 is about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the retention time of des-*t*-butyl-goserelin is between 19 and 22 minutes.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1) the area of the peak corresponding to impurity 13 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

The sum of impurities obtained in test B and impurity 13 in test C is not more than 10%.

Acetic acid

Carry out the method for *gas chromatography*, Appendix III B, using a 2% v/v solution of n-*hexadecane* (internal standard) in *dimethylformamide* (solution B) and the following solutions.

(1) Dissolve a quantity of the implant and a quantity of solution B and dilute with sufficient *dimethylformamide* to obtain a solution containing about 2.8% w/v of Goserelin Implant and 0.1% v/v of n-*hexadecane*.

(2) Prepare a solution containing 0.625% w/v of *glacial acetic acid* in *dimethylformamide*. To 10 mL of this solution add 5 mL of solution B and dilute to 100 mL with *dimethylformamide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a free fatty acid phase capillary column (10 m × 0.32 mm) with a nominal film thickness of 0.2 to 0.3 µm (FFAP CB is suitable).

(b) Use *helium* as the carrier gas at a flow rate of 1.3 mL per minute with a flow rate of the make up gas of 30 mL per minute.

(c) Use the gradient conditions described below.

(d) Use an injection temperature of 200°

(d) Use a flame ionisation detector at a temperature of 250°.

(e) Inject 1 µL of each solution.

(f) Use a split ratio of 30:100.

Time (Minutes)	Temperature	Comment
0→1	50°	isothermal
1→6	50°→200°	linear gradient
6→9	200°	isothermal
9→10	200°→50°	linear gradient
10-15	50°	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2):

the *resolution* between the peaks due to *acetic acid* and n-*hexadecane* is at least 15;

the *symmetry factor* of the peak due to acetic acid is less than 2.0.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1) the ratio of the area of any peak corresponding to acetic acid to the area of the peak due to the internal standard is not greater than the corresponding ratio in the chromatogram obtained with solution (2) (2.5%).

Water

Not more than 2.5% w/w, Appendix IX C. Use Method III. Prepare the sample by dissolving approximately 110 mg of the implant in 4 mL of dry *dimethylformamide*.

Bacterial endotoxins

Carry out the *test for bacterial endotoxins*, Appendix XIV C. Dissolve the copolymer using 2 mL of *acetonitrile* per implant and dilute to a suitable concentration with *water BET* (solution A). The endotoxin limit concentration of solution A is 350 IU of endotoxin per implant.

Uniformity of content

The implants comply with the limits described in test A for *uniformity of content*, Appendix XII C, using the following method of analysis.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve with the aid of ultrasound, 1 implant in a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile* to obtain a solution containing 0.02% w/v of Goserelin.
(2) 0.02% w/v of *goserelin EPCRS* in a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile*.
(3) 0.02% w/v each of *goserelin hexapeptide BPCRS* and *goserelin EPCRS* in a mixture of 4 volumes of *water* and 1 volume of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.8 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 220 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

0.272% w/v of *potassium dihydrogen orthophosphate* in a mixture of 45 volumes of *water* and 55 volumes of *methanol*. Adjust the pH to 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to goserelin hexapeptide and goserelin is not less than 4.0.

DETERMINATION OF CONTENT

www.webofpharma.com

https://thuocngocanh.com/

Calculate the total content of goserelin, $C_{59}H_{84}N_{18}O_{14}$, from the chromatograms obtained and using the declared content of $C_{59}H_{84}N_{18}O_{14}$ in *goserelin EPCRS*.

ASSAY

Carry out the method for *size-exclusion chromatography*, Appendix III C, using the following solutions.

(1) Weigh and dissolve 10 implants, with the aid of ultrasound, in a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile* to obtain a solution containing 0.2% w/v of Goserelin.

(2) 0.2% w/v of *goserelin EPCRS* in a mixture of 15 volumes of *water* and 85 volumes of *acetonitrile*.

(3) 0.002% w/v each of *4-D-Ser-goserelin EPCRS* and *goserelin EPCRS* in a mixture of 20 volumes of water and 80 volumes of *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances test B, may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to 4-D-Ser-goserelin and goserelin is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of goserelin, $C_{59}H_{84}N_{18}O_{14}$, from the chromatograms obtained and using the declared content of $C_{59}H_{84}N_{18}O_{14}$ in *goserelin EPCRS*.

STORAGE

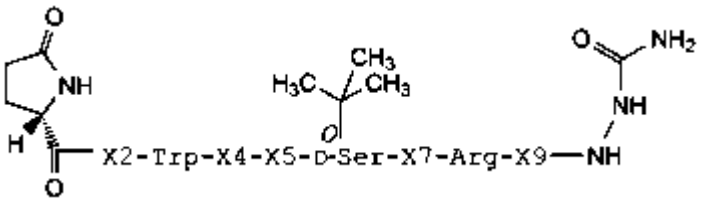
Goserelin Implants should be stored in a sealed container, protected from light and moisture, at a temperature not exceeding 25°.

LABELLING

The label states the equivalent amount of the peptide in mg in each implant.

IMPURITIES

The impurities controlled by this monograph include:



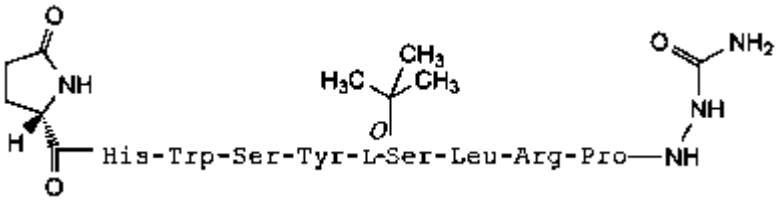
1. X2 = L-His, X4 = D-Ser, X5 = L-Tyr, X7 = L-Leu, X9 = L-Pro: 4(D-serine)-goserelin (equivalent to *Ph. Eur.* impurity A),

6. X2 = L-His, X4 = L-Ser, X5 = D-Tyr, X7 = L-Leu, X9 = L-Pro: 5(D-tyrosine)-goserelin (equivalent to *Ph. Eur.* impurity F),

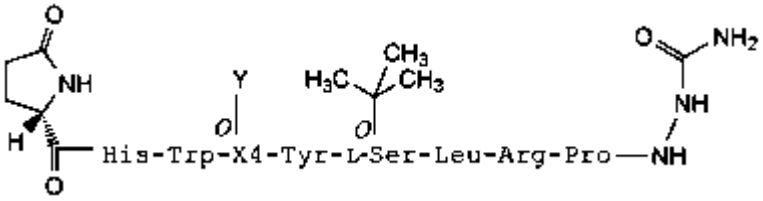
www.webofpharma.com

https://thuocngocanh.com/

12. X2 = L-His, X4 = L-Ser, X5 = L-Tyr, X7 = D-Leu, X9 = L-Pro: 7(D-leucine)-goserelin (equivalent to *Ph. Eur.* impurity L),



2. 6-[*O*-(1,1-dimethylethyl)-L-serine]-goserelin (equivalent to *Ph. Eur.* impurity B),



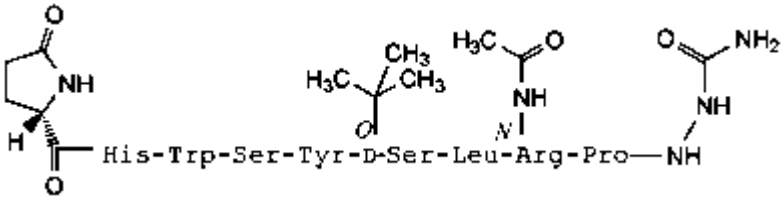
3. X4 = L-Ser, Y = Acetyl: 4-(acetyl-L-serine)-goserelin,

4. X4 = D-Ser, Y = Acetyl: 4-(acetyl-D-serine)-goserelin,

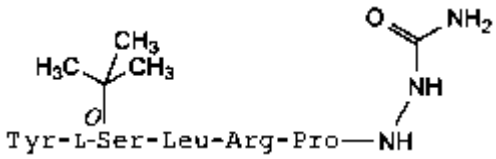
5. X4 = L-Ser, Y = Lactyl: 4-(lactyl-L-serine)-goserelin,

11. X4 = L-Ser, Y = Glycolyl: 4-(glycolyl-L-serine)-goserelin,

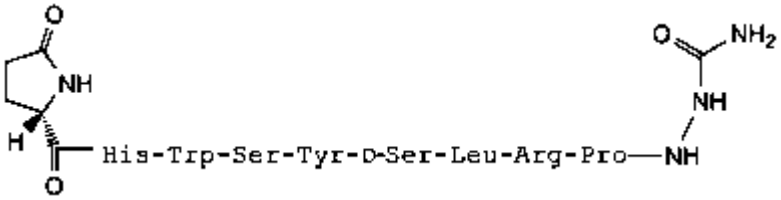
7. X4 = L-Ser, Y = Lactide/Glycolide copolymer chain: Polymer envelope,



8. 8-(N-acetylamino-L-arginine)-goserelin,



9. Hexapeptide,



10. 6-(des-*t*-butyl-D-serine)-goserelin,

13. The structure of this peak has not been identified.

www.webofpharma.com

https://thietbiluocngocanh.com/

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

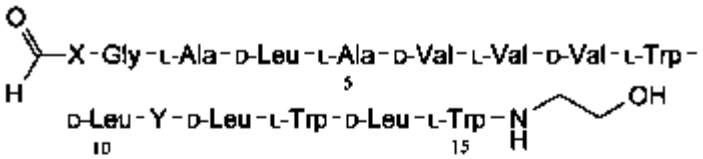
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

This text was updated in Ph. Eur. 11.0 (effective 01/01/2023)

Gramicidin

General Notices

(Ph. Eur. monograph 0907)



Gramicidin	X	Y	Mol. formula	M_r
A1	L-Val	L-Trp	$C_{99}H_{140}N_{20}O_{17}$	1882
A2	L-Ile	L-Trp	$C_{100}H_{142}N_{20}O_{17}$	1896
B1	L-Val	L-Phe	$C_{97}H_{139}N_{19}O_{17}$	1843
C1	L-Val	L-Tyr	$C_{97}H_{139}N_{19}O_{18}$	1859
C2	L-Ile	L-Tyr	$C_{98}H_{141}N_{19}O_{18}$	1873

Action and use

Polypeptide antibacterial.

Ph Eur

DEFINITION

Gramicidin consists of a family of antimicrobial linear polypeptides, usually obtained by extraction from tyrothricin, the complex isolated from the fermentation broth of *Brevibacillus brevis* Dubos. The main component is gramicidin A1, together with gramicidins A2, B1, C1 and C2 in particular.

Content

Minimum 900 IU/mg (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, slightly hygroscopic.

www.webofpharma.com

https://thuocngocanh.com/

Solubility

Practically insoluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent).

mp

About 230 °C.

IDENTIFICATION

First identification: A, C.

Second identification: A, B.

A. Dissolve 0.100 g in *alcohol R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *alcohol R*. Examined between 240 nm and 320 nm (*2.2.25*), the solution shows 2 absorption maxima, at 282 nm and 290 nm, a shoulder at about 275 nm and an absorption minimum at 247 nm. The specific absorbance at the maximum at 282 nm is 105 to 125.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 5 mg of the substance to be examined in 6.0 mL of *alcohol R*.

Reference solution (a) Dissolve 5 mg of *gramicidin CRS* in 6.0 mL of *alcohol R*.

Reference solution (b) Dissolve 5 mg of *tyrothricin CRS* in 6.0 mL of *alcohol R*.

Plate *TLC silica gel plate R*.

Mobile phase *methanol R*, *butanol R*, *water R*, *glacial acetic acid R*, *butyl acetate R* (3:9:15:24:49 *V/V/V/V/V*).

Application 1 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Dip the plate into *dimethylaminobenzaldehyde solution R2*. Heat at 90 °C until the spots appear.

System suitability The chromatogram obtained with reference solution (b) shows 2 clearly separated spots or 2 clearly separated groups of spots.

Results The principal spot or group of principal spots in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot or group of principal spots in the chromatogram obtained with reference solution (a) and to the spot or group of spots with the highest R_F value in the chromatogram obtained with reference solution (b).

C. Examine the chromatograms obtained in the test for composition.

Results The 3 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the 3 principal peaks in the chromatogram obtained with reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

TESTS

Composition

Liquid chromatography (2.2.29): use the normalisation procedure.

Test solution Dissolve 25 mg of the substance to be examined in 10 mL of *methanol R* and dilute to 25 mL with the mobile phase.

Reference solution (a) Dissolve 25 mg of *gramicidin CRS* in 10 mL of *methanol R* and dilute to 25 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm,

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm),

— *temperature*: 50 °C.

Mobile phase *water R*, *methanol R* (29:71 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 282 nm.

Injection 20 µL.

Run time 2.5 times the retention time of gramicidin A1.

Relative retention With reference to gramicidin A1 (retention time = about 22 min): gramicidin C1 = about 0.7; gramicidin C2 = about 0.8; gramicidin A2 = about 1.2; gramicidin B1 = about 1.9.

System suitability Reference solution (a):

— *resolution*: minimum 1.5 between the peaks due to gramicidin A1 and gramicidin A2,

— the chromatogram obtained is concordant with the chromatogram supplied with *gramicidin CRS*.

Limits:

— *sum of gramicidins A1, A2, B1, C1 and C2*: minimum 95.0 per cent,

— *ratio of gramicidin A1 to the sum of gramicidins A1, A2, B1, C1 and C2*: minimum 0.60,

— *disregard limit*: the area of the peak due to gramicidin A1 in the chromatogram obtained with reference solution (b).

Related substances

www.webofpharma.com

https://thuocngocanh.com/

Liquid chromatography (*2.2.29*) as described in the test for composition.

Limit:

— *any impurity*: maximum 2.0 per cent and not more than 1 peak is more than 1.0 per cent; disregard the peaks due to gramicidins A1, A2, B1, C1 and C2.

Loss on drying (*2.2.32*)

Maximum 3.0 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa for 3 h.

Sulfated ash (*2.4.14*)

Maximum 1.0 per cent, determined on 1.0 g.

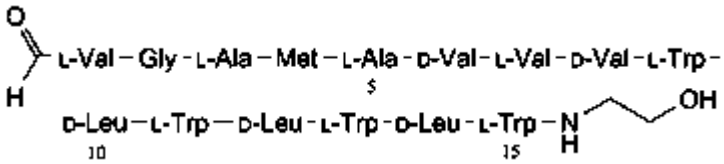
ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*), using the turbidimetric method. Use *gramicidin CRS* as the reference substance.

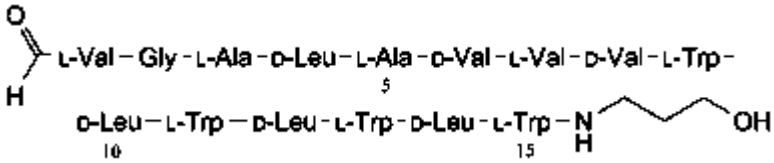
STORAGE

In an airtight container, protected from light.

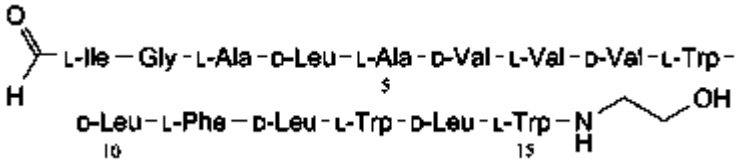
IMPURITIES



A. [4-methionine]gramicidin A1,



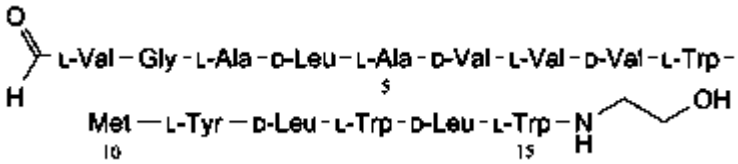
B. gramicidin A1 3-hydroxypropyl,



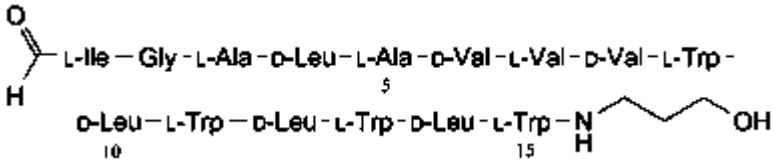
C. gramicidin B2,

www.webofpharma.com

https://thuocngocanh.com/



D. [10-methionine]gramicidin C1,



E. gramicidin A2 3-hydroxypropyl.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

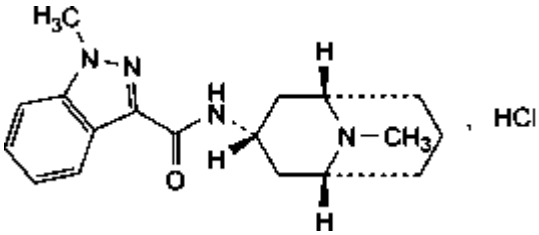
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Granisetron Hydrochloride

General Notices

(Ph. Eur. monograph 1695)



$C_{18}H_{25}ClN_4O$ 348.9 *107007-99-8*

Action and use

Serotonin $5HT_3$ receptor antagonist; treatment of nausea and vomiting.

Ph Eur

DEFINITION

1-Methyl-*N*-[(1*R*,3*r*,5*S*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide hydrochloride.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, sparingly soluble in methylene chloride, slightly soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *granisetron hydrochloride CRS*.

www.webofpharma.com

https://thuocngocanh.com/

B. It gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.2 g in carbon dioxide-free water R and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

pH (2.2.3)

4.0 to 6.5 for solution S.

Impurity E

Thin-layer chromatography (2.2.27).

Solvent mixture water R, acetonitrile R (20:80 *V/V*).

Test solution Dissolve 0.25 g of the substance to be examined in the solvent mixture and dilute to 5 mL with the solvent mixture.

Reference solution Dissolve 5.0 mg of granisetron impurity E CRS in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Plate TLC silica gel F_{254} plate R.

Mobile phase concentrated ammonia R, 2-propanol R, ethyl acetate R (6.5:30:50 *V/V/V*).

Application 2 µL.

Development Over half of the plate.

Drying In air.

Detection Expose to iodine vapour for 30 min.

Limit:

— *impurity E*: any spot due to impurity E is not more intense than the principal spot in the chromatogram obtained with the reference solution (0.5 per cent).

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b) Transfer 2 mL of the test solution to a colourless glass vial, stopper and expose the solution either to sunlight for 4 h or place under a UV lamp for 16 h (partial degradation of granisetron to impurity C). A degradation of at least about 0.3 per cent of granisetron to impurity C must be obtained as shown by appearance of a corresponding peak in the chromatogram. If not, expose the solution once again to sunlight or place under a UV lamp.

Reference solution (c) Dissolve 50.0 mg of *granisetron hydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (d) Dissolve the contents of a vial of *granisetron impurity A CRS* in 1 mL of the mobile phase.

Reference solution (e) Dissolve the contents of a vial of *granisetron impurity B CRS* in 1 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Dilute 1.6 mL of *phosphoric acid R* to 800 mL with *water for chromatography R*, add 200 mL of *acetonitrile R* and mix. Add 1.0 mL of *hexylamine R* and mix. Adjust to pH 7.5 ± 0.05 with freshly distilled *triethylamine R* (about 4 mL).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 305 nm.

Injection 10 µL of the test solution and reference solutions (a), (b), (d) and (e).

Run time Twice the retention time of granisetron.

Relative retention With reference to granisetron (retention time = about 7 min): impurity D = about 0.4; impurity B = about 0.5; impurity A = about 0.7; impurity C = about 0.8.

System suitability:

— *resolution*: minimum 3.5 between the peaks due to impurity C and granisetron in the chromatogram obtained with reference solution (b);

— *symmetry factor*: maximum 2.0 for the peak due to granisetron in the chromatogram obtained with reference solution (a).

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 1.7;

— *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

www.webofpharma.com

https://thuocngocanh.com/

— *impurity C*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *impurity D*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (2.2.32)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

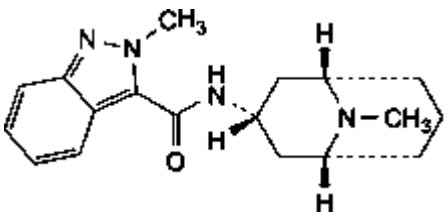
Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{18}H_{25}ClN_4O$ taking into account the assigned content of *granisetron hydrochloride CRS*.

IMPURITIES

Specified impurities *A, B, C, D, E.*

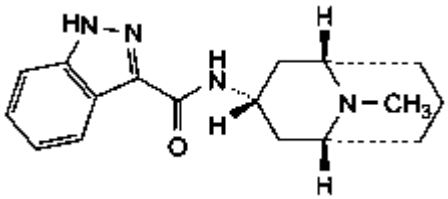
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *F, G, H, I.*



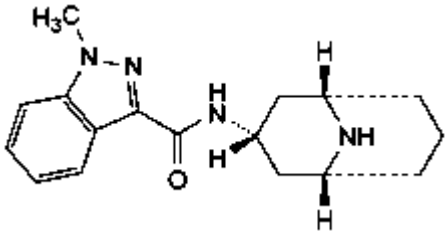
A. 2-methyl-*N*-[(1*R*,3*r*,5*S*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-2*H*-indazole-3-carboxamide,

www.webofpharma.com

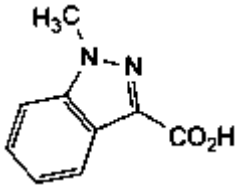
https://thuocngocanh.com/



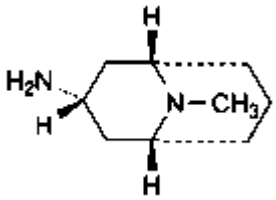
B. *N*-[(1*R*,3*r*,5*S*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide,



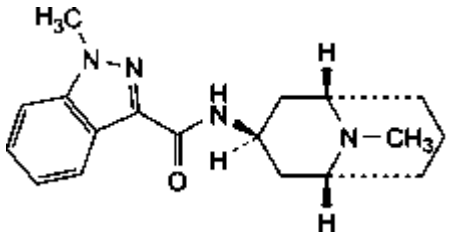
C. *N*-[(1*R*,3*r*,5*S*)-9-azabicyclo[3.3.1]non-3-yl]-1-methyl-1*H*-indazole-3-carboxamide,



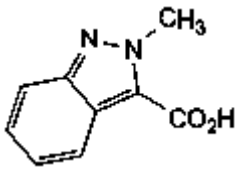
D. 1-methyl-1*H*-indazole-3-carboxylic acid,



E. (1*R*,3*r*,5*S*)-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine,



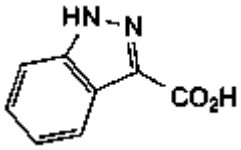
F. 1-methyl-*N*-[(1*R*,3*s*,5*S*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1*H*-indazole-3-carboxamide (*exo*-granisetron),



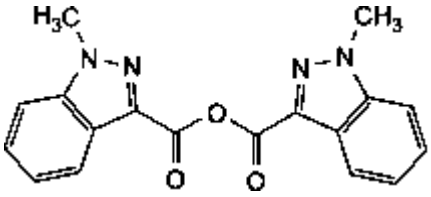
G. 2-methyl-2*H*-indazole-3-carboxylic acid,

www.webofpharma.com

https://thuocngocanh.com/



H. 1*H*-indazole-3-carboxylic acid,



I. 1-methyl-1*H*-indazole-3-carboxylic anhydride.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

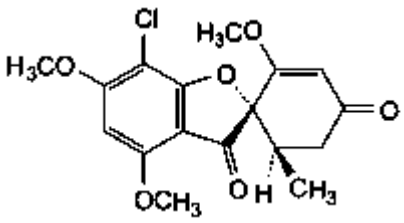
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Griseofulvin

General Notices

(Ph. Eur. monograph 0182)



$C_{17}H_{17}ClO_6$ 352.8 *126-07-8*

Action and use

Antifungal.

Preparation

Griseofulvin Tablets

Ph Eur

DEFINITION

(1′*S*,6′*R*)-7-Chloro-2′,4,6-trimethoxy-6′-methyl-3*H*-spiro[1-benzofuran-2,1′-cyclohex[2]ene]-3,4′-dione.

Substance produced by the growth of certain strains of *Penicillium griseofulvum*.

Content

94.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or yellowish-white powder.

Solubility

Practically insoluble in water, freely soluble in dimethylformamide, slightly soluble in anhydrous ethanol and in methanol.

It shows polymorphism (*5.9*).

www.webofpharma.com

https://thuocngocanh.com/

mp

About 220 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *griseofulvin for LC assay and identification CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_4 (*2.2.2, Method II*).

Dissolve 0.75 g in *dimethylformamide R* and dilute to 10 mL with the same solvent.

Acidity

Suspend 0.25 g in 20 mL of *ethanol (96 per cent) R* and add 0.1 mL of *phenolphthalein solution R*. Not more than 1.0 mL of *0.02 M sodium hydroxide* is required to change the colour of the indicator.

Specific optical rotation (*2.2.7*)

+ 354 to + 364 (dried substance).

Dissolve 0.250 g in *dimethylformamide R* and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in mobile phase B and dilute to 50.0 mL with mobile phase B.

Reference solution (a) Dissolve 25.0 mg of *griseofulvin for LC assay and identification CRS* in mobile phase B and dilute to 50.0 mL with mobile phase B.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase B.

Reference solution (c) Dissolve 5 mg of *griseofulvin for system suitability CRS* (containing impurities A, B and C) in mobile phase B and dilute to 10 mL with mobile phase B.

Column:

www.webofpharma.com

https://thuocngocanh.com/

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: mix 20 volumes of a 0.1 per cent *V/V* solution of *anhydrous formic acid R* previously adjusted to pH 4.5 with *dilute ammonia R2* and 80 volumes of *water for chromatography R*;

— *mobile phase B*: mix 15 volumes of *water for chromatography R*, 20 volumes of a 0.1 per cent *V/V* solution of *anhydrous formic acid R* previously adjusted to pH 4.5 with *dilute ammonia R2* and 65 volumes of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	50	50
3 - 13	50 → 40	50 → 60
13 - 16	40 → 10	60 → 90
16 - 24	10	90

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 290 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and C.

Relative retention With reference to griseofulvin (retention time = about 16 min): impurity A = about 0.4; impurity B = about 0.7; impurity C = about 1.1.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to griseofulvin.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity A by 0.6;

— for each impurity, use the concentration of griseofulvin in reference solution (b).

Limits:

www.webofpharma.com

https://thuocngocanh.com/

— *impurity B*: maximum 3.0 per cent;

— *impurity A*: maximum 2.0 per cent;

— *impurity C*: maximum 0.75 per cent;

— *unspecified impurities*: for each impurity, maximum 0.15 per cent;

— *total*: maximum 5.0 per cent;

— *reporting threshold*: 0.10 per cent.

Loss on drying (2.2.32)

Maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14)

Maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (a).

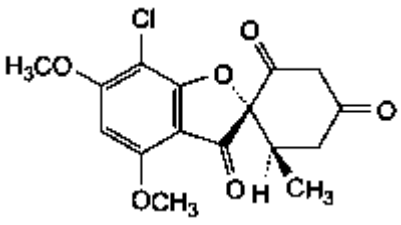
System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 2.0 per cent determined on 6 injections.

Calculate the percentage content of $C_{17}H_{17}ClO_6$ taking into account the assigned content of *griseofulvin for LC assay and identification CRS*.

IMPURITIES

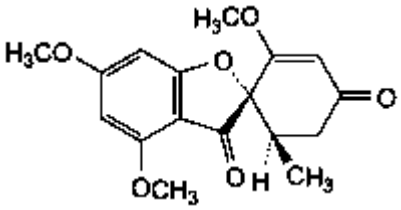
Specified impurities *A, B, C*.



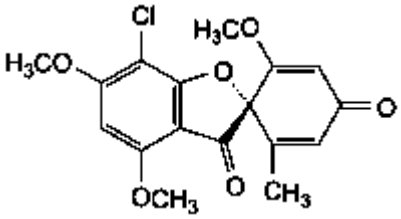
A. (1′*S*,6′*R*)-7-chloro-4,6-dimethoxy-6′-methyl-3*H*-spiro[1-benzofuran-2,1′-cyclohexane]-2′,3,4′-trione,

www.webofpharma.com

https://thuvienthuocngocanh.com/



B. (1′*S*,6′*R*)-2′,4,6-trimethoxy-6′-methyl-3*H*-spiro[1-benzofuran-2,1′-cyclohex[2]ene]-3,4′-dione,



C. (1′*S*)-7-chloro-2′,4,6-trimethoxy-6′-methyl-3*H*-spiro[1-benzofuran-2,1′-cyclohexa[2,5]diene]-3,4′-dione.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Griseofulvin Tablets

General Notices

Action and use

Antifungal.

DEFINITION

Griseofulvin Tablets contain Griseofulvin.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of griseofulvin, $C_{17}H_{17}ClO_6$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.125 g of Griseofulvin with 20 mL of *dichloromethane*, add 1 g of *anhydrous sodium sulfate*, shake and filter. Evaporate the filtrate to dryness and dry at a pressure not exceeding 0.7 kPa for 1 hour. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of griseofulvin *(RS 172)*.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.

(b) Use 1000 mL of a 1.5% w/v solution of *sodium dodecyl sulfate*, at a temperature of 37°, as the medium.

PROCEDURE

After 45 minutes withdraw a 10-mL sample of the medium and filter. Measure the *absorbance* of the filtrate, suitably diluted if necessary with *methanol (80%)*, at the maximum at 291 nm, Appendix II B, using a 1.5% w/v solution of *sodium dodecyl sulfate* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of griseofulvin, $C_{17}H_{17}ClO_6$, in the medium taking 725 as the value of A(1%, 1 cm) at the maximum at 291 nm.

LIMITS

www.webofpharma.com

https://thuocngocanh.com/

The amount of griseofulvin released is not less than 75% of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mobile phase B.

(1) Disperse a quantity of powdered tablets containing 0.25 g of Griseofulvin in mobile phase B and dilute to 500 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes.

(3) 0.05% w/v of *griseofulvin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Discovery C18 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 20 volumes of 0.1 % v/v *formic acid* adjusted to pH 4.5 with *dilute ammonia R2* and 80 volumes of *water*.

Mobile phase B 15 volumes of *water*, 20 volumes of 0.1 % v/v *formic acid* adjusted to pH 4.5 with *dilute ammonia R2* and 65 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	50	50	isocratic
3-13	50→40	50→60	linear gradient
13-16	40→10	60→90	linear gradient
16-24	10	90	isocratic

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to griseofulvin (retention time about 16 minutes) are: impurity A, about 0.4; impurity B, about 0.7 and impurity C, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 3.0, where *Hp* is the height above the baseline of the peak due to impurity C and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to griseofulvin.

LIMITS

Identify any peak corresponding to impurity A in the chromatogram obtained with solution (1) and multiply the area of this peak by a correction factor of 0.6.

www.webofpharma.com

https://thuocngocanh.com/

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

the area of any peak corresponding to impurity C is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%);

the area of any other *secondary peak* is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (5.0%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) Disperse a quantity of powdered tablets containing 0.25 g of Griseofulvin in mobile phase B and dilute to 500 mL.
(2) 0.05% w/v of *griseofulvin for LC assay and identification EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{17}ClO_6$ in the tablets from the chromatograms obtained and using the declared content of $C_{17}H_{17}ClO_6$ in *griseofulvin EPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Griseofulvin.

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

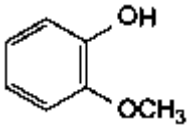
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Guaiacol

General Notices

(Ph. Eur. monograph 1978)



$C_7H_8O_2$ 124.1 *90-05-1*

Ph Eur

DEFINITION

2-Methoxyphenol.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Crystalline mass or colourless or yellowish liquid, hygroscopic.

Solubility

Sparingly soluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 per cent).

mp

About 28 °C.

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry (*2.2.24*).

www.webofpharma.com

https://thuocngocanh.com/

Comparison *guaiacol CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.5 g of the substance to be examined in *methanol R* and dilute to 25 mL with the same solvent.

Reference solution Dissolve 0.5 g of *guaiacol CRS* in *methanol R* and dilute to 25 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *anhydrous acetic acid R*, *methanol R*, *toluene R* (6:14:80 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with *ferric chloride solution R1*.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 1.00 g in *ethanol (96 per cent) R* and dilute to 10.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method I*).

Acidity or alkalinity

To 5.0 mL of solution S, add 10 mL of *carbon dioxide-free water R* and 0.1 mL of *methyl red mixed solution R*. Not more than 0.05 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Impurity A

Liquid chromatography (*2.2.29*).

Solvent mixture *phosphoric acid R*, *water R*, *methanol R* (1:499:500 *V/V/V*).

Test solution (a) Dissolve 1.0 g of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dissolve 0.20 g of *pyrocatechol R* (impurity A) and 0.20 g of *phenol R* (impurity B) in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of this solution to 10 mL with the solvent mixture.

Reference solution (c) Dissolve 20.0 mg of *guaiacol CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *methanol R*, *water R* (1:150:849 *V/V/V*);

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 28	100	0
28 - 30	100 → 35	0 → 65
30 - 40	35	65

Flow rate 1 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Retention time Guaiacol = about 20 min.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to impurities A (1st peak) and B (2nd peak).

Limit:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Related substances

Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution Dissolve 1.00 g of the substance to be examined in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

Reference solution (a) Dissolve 0.20 g of *phenol R* (impurity B) and 0.40 g of *methyl benzoate R* (impurity E) in *acetonitrile R* and dilute to 50 mL with the same solvent. Dilute 1 mL of this solution to 20 mL with *acetonitrile R*.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (b) Dilute 0.5 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (c) Dissolve 10 mg of *veratrole R* (impurity C) in *acetonitrile R* and dilute to 10 mL with the same solvent.

Column:

— *material*: fused silica;

— *size*: *l* = 25 m, Ø = 0.53 mm;

— *stationary phase*: *cyanopropyl(7)phenyl(7)methyl(86)polysiloxane R* (film thickness 2 µm).

Carrier gas *helium for chromatography R*.

Flow rate 5 mL/min.

Split ratio 1:5.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 15	90
	15 - 45	90 → 180
Injection port		200
Detector		220

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to guaiacol (retention time = about 25 min): impurity E = about 0.88; impurity B = about 0.92; impurity C = about 1.1.

System suitability Reference solution (a):

— *resolution*: minimum 2.0 between the peaks due to impurities E (1st peak) and B (2nd peak).

Limits:

— *impurity C*: maximum 0.4 per cent;

— *impurity E*: maximum 0.2 per cent;

— *impurity B*: maximum 0.15 per cent;

www.webofpharma.com

https://thuocngocanh.com/

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 2.000 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for impurity A with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_7H_8O_2$ from the declared content of *guaiacol CRS*.

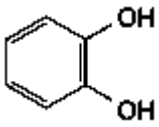
STORAGE

In an airtight container, protected from light.

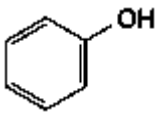
IMPURITIES

Specified impurities *A, B, C, E.*

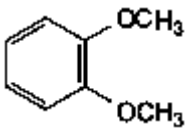
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *D, F, G, H.*



A. benzene-1,2-diol (pyrocatechol),



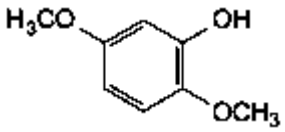
B. phenol,



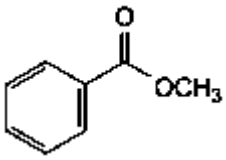
www.webofpharma.com

https://thuocngocanh.com/

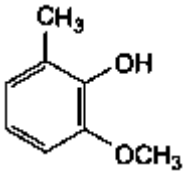
C. 1,2-dimethoxybenzene (veratrole),



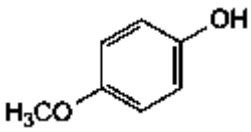
D. 2,5-dimethoxyphenol,



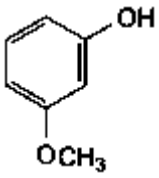
E. methyl benzoate,



F. 2-methoxy-6-methylphenol (6-methylguaiacol),



G. 4-methoxyphenol,



H. 3-methoxyphenol.

Ph Eur

© Crown Copyright 2022

Medicines & Healthcare products Regulatory Agency

www.webofpharma.com

https://thuocngocanh.com/

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

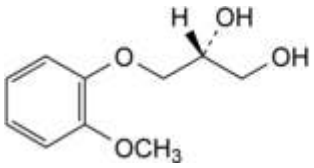
https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Guaifenesin

General Notices

(Ph. Eur. monograph 0615)



and enantiomer

$C_{10}H_{14}O_4$ 198.2 *93-14-1*

Action and use

Expectorant.

Ph Eur

DEFINITION

(2*RS*)-3-(2-Methoxyphenoxy)propane-1,2-diol.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (*2.2.14*): 79 °C to 83 °C.

www.webofpharma.com

https://thuocngocanh.com/

B. Infrared absorption spectrophotometry (2.2.24).

Comparison guaifenesin CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 30 mg of the substance to be examined in methanol R and dilute to 10 mL with the same solvent.

Reference solution Dissolve 30 mg of guaifenesin CRS in methanol R and dilute to 10 mL with the same solvent.

Plate TLC silica gel plate R.

Mobile phase methylene chloride R, 2-propanol R (20:80 *V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a solution, prepared immediately before use, containing 0.4 g of dimethylaminobenzaldehyde R in an ice-cooled mixture of 10 mL of water R and 10 mL of hydrochloric acid R; allow to dry in air and heat at 105 °C for 10 min; examine under white light.

Results The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S

Dissolve 1.0 g in carbon dioxide-free water R, heating gently if necessary, and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity

To 10 mL of solution S add 0.05 mL of phenolphthalein solution R1. Not more than 0.1 mL of 0.01 M sodium hydroxide is required to change the colour of the indicator. To 10 mL of solution S add 0.15 mL of methyl red solution R. Not more than 0.1 mL of 0.01 M hydrochloric acid is required to change the colour of the indicator to red.

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.100 g of the substance to be examined in water R and dilute to 50.0 mL with the same solvent.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in water R and dilute to 50.0 mL with the same solvent.

www.webofpharma.com

https://thuocngocanh.com/

Reference solution (a) Dilute 1.0 mL of test solution (a) to 50.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 50.0 mg of *guaiacol R* (impurity A) in *water R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 10.0 mL with test solution (a).

Reference solution (c) Dissolve 5.0 mg of *guaifenesin for peak identification CRS* (containing impurities B, C and D) in *water R* and dilute to 5.0 mL with the same solvent.

Reference solution (d) Dissolve 25.0 mg of *guaifenesin CRS* in *water R* and dilute to 50.0 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *glacial acetic acid R*, *water for chromatography R* (1:99 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 34	80 → 50	20 → 50

Flow rate 1 mL/min.

Detection Spectrophotometer at 276 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, C and D.

Relative retention With reference to guaifenesin (retention time = about 8 min): impurity B = about 0.9; impurity A = about 1.4; impurity C = about 3.1; impurity D = about 3.7.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to guaifenesin and impurity A.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 0.7;

— for each impurity, use the concentration of guaifenesin in reference solution (a).

www.webofpharma.com

https://thuocngocanh.com/

Limits:

— *impurity B*: maximum 0.5 per cent;

— *impurities C, D*: for each impurity, maximum 0.1 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total:* maximum 0.7 per cent;

— *reporting threshold*: 0.03 per cent.

Chlorides and monochlorhydrins

Maximum 250 ppm.

To 10 mL of solution S add 2 mL of *dilute sodium hydroxide solution R* and heat on a water-bath for 5 min. Cool and add 3 mL of *dilute nitric acid R*. The resulting solution complies with the limit test for chlorides (*2.4.4*).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

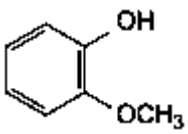
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{10}H_{14}O_4$ taking into account the assigned content of *guaifenesin CRS*.

IMPURITIES

Specified impurities *B, C, D.*

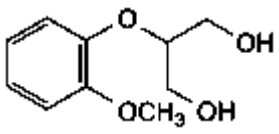
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A.*



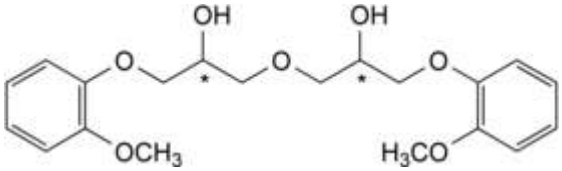
www.webofpharma.com

https://thuocngocanh.com/

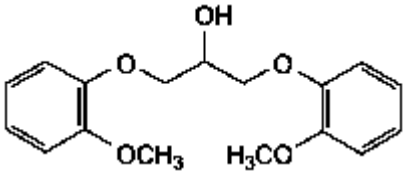
A. 2-methoxyphenol (guaiacol),



B. 2-(2-methoxyphenoxy)propane-1,3-diol (B-isomer),



C. 1,1′-oxybis[3-(2-methoxyphenoxy)propan-2-ol] (bisether),



D. 1,3-bis(2-methoxyphenoxy)propan-2-ol.

Ph Eur

© Crown Copyright 2022

Contact us | Latest news | Subscribe | Back to the top

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com

https://thuocngocanh.com/

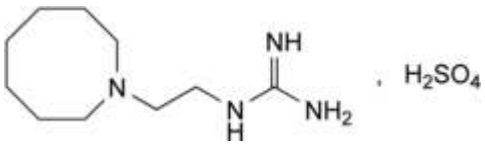
You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Guanethidine Monosulfate

General Notices

Guanethidine Monosulphate

(Ph. Eur. monograph 0027)



$C_{10}H_{24}N_4O_4S$ 296.4 *645-43-2*

Action and use

Adrenergic neuron blocker.

Ph Eur

DEFINITION

1-[2-(Hexahydroazocin-1(2*H*)-yl)ethyl]guanidine monosulfate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Colourless, crystalline powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent).

mp

About 250 °C, with decomposition.

IDENTIFICATION

www.webofpharma.com

https://thuocngocanh.com/

A. Dissolve about 25 mg in 25 mL of *water R*, add 20 mL of *picric acid solution R* and filter. The precipitate, washed with *water R* and dried at 100-105 °C, melts (*2.2.14*) at about 154 °C.

B. Dissolve about 25 mg in 5 mL of *water R*. Add 1 mL of *strong sodium hydroxide solution R*, 1 mL of *α-naphthol solution R* and, dropwise with shaking, 0.5 mL of *strong sodium hypochlorite solution R*. A bright pink precipitate is formed and becomes violet-red on standing.

C. It gives the reactions of sulfates (*2.3.1*).

TESTS

Solution S

Dissolve 0.4 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Appearance of solution

Solution S is not more intensely coloured than reference solution GY_6 (*2.2.2, Method II*).

pH (*2.2.3*)

4.7 to 5.5 for solution S.

Oxidisable substances

In a conical, ground-glass-stoppered flask, dissolve 1.0 g in 25 mL of *water R* and add 25 mL of *dilute sodium hydroxide solution R*. Allow to stand for 10 min and add 1 g of *potassium bromide R* and 1 mL of 0.0083 M potassium bromate. Acidify with 30 mL of *dilute hydrochloric acid R*. Mix and allow to stand in the dark for 5 min. Add 2 g of *potassium iodide R* and shake. Allow to stand for 2 min and titrate the liberated iodine with *0.05 M sodium thiosulfate*, using *starch solution R* as indicator. Not less than 0.3 mL of *0.05 M sodium thiosulfate* is required to decolorise the solution.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.00 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g, warming if necessary, in 30 mL of *anhydrous acetic acid R* and add 15 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 29.64 mg of $C_{10}H_{24}N_4O_4S$.

STORAGE

www.webofpharma.com

https://thietbiuocngocanh.com/

Protected from light.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Guar

General Notices

(Ph. Eur. monograph 1218)

Ph Eur

DEFINITION

Guar is obtained by grinding the endosperms of seeds of *Cyamopsis tetragonolobus* (L.) Taub. It consists mainly of guar galactomannan.

CHARACTERS

Appearance

White or almost white powder.

Solubility

It yields a mucilage of variable viscosity when dissolved in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Examined under a microscope in *glycerol R*, the substance to be examined (125) (*2.9.12*) shows pyriform or ovoid cells, usually isolated, having very thick walls around a central somewhat elongated lumen with granular contents, and smaller polyhedral cells, isolated or in clusters, with thinner walls.

B. In a conical flask place 2 g, add rapidly 45 mL of *water R* and stir vigorously for 30 s. After 5-10 min a stiff gel forms which does not flow when the flask is inverted.

C. Mix a suspension of 0.1 g in 10 mL of *water R* with 1 mL of a 10 g/L solution of *disodium tetraborate R*; the mixture soon gels.

D. Thin-layer chromatography (*2.2.27*).

Test solution To 10 mg of the substance to be examined in a thick-walled centrifuge tube add 2 mL of a 100 g/L solution of *trifluoroacetic acid R*, shake vigorously to dissolve the forming gel, stopper the tube and heat the mixture at 120 °C for 1 h. Centrifuge the hydrolysate, transfer the clear supernatant carefully into a 50 mL flask, add 10 mL of *water R* and evaporate the solution to dryness under reduced pressure. To the resulting clear film add 0.1 mL of *water R* and 0.9 mL of *methanol R*. Centrifuge to separate the amorphous precipitate. Dilute the supernatant, if necessary, to 1 mL with *methanol R*.

Reference solution Dissolve 10 mg of *galactose R* and 10 mg of *mannose R* in 2 mL of *water R*, then dilute to 20 mL with *methanol R*.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *acetonitrile R* (15:85 *V/V*).

www.webofpharma.com

https://thietbiuocngocanh.com/

Application 5 µL, as bands.

Development Over a path of 15 cm.

Detection Spray with *aminohippuric acid reagent R* and dry at 120 °C for 5 min.

Results The chromatogram obtained with the reference solution shows in the lower part 2 clearly separated brownish zones due to galactose and mannose in order of increasing R_F value; the chromatogram obtained with the test solution shows 2 zones due to galactose and mannose.

TESTS

Tragacanth, sterculia gum, agar, alginates, carrageenan

To a small amount of the substance to be examined add 0.2 mL of freshly prepared *ruthenium red solution R*. Examined under a microscope the cell walls do not stain red.

Protein

Maximum 8.0 per cent.

Carry out the determination of nitrogen by sulfuric acid digestion (*2.5.9*), using 0.170 g. Multiply the result by 6.25.

Apparent viscosity (*2.2.10*)

85 per cent to 115 per cent of the value stated on the label.

Moisten a quantity equivalent to 1.00 g of the dried substance with 2.5 mL of *2-propanol R*. While stirring, dilute to 100.0 mL with *water R*. After 1 h, determine the viscosity at 20 °C using a rotating viscometer and a shear rate of 100 s^{-1}.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 5 h.

Total ash (*2.4.16*)

Maximum 1.8 per cent.

Microbial contamination

TAMC: acceptance criterion 10^4 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

www.webofpharma.com

https://thuocngocanh.com/

LABELLING

The label states the apparent viscosity in millipascal seconds for a 10 g/L solution.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for guar used as viscosity-increasing agent or binder.

Apparent viscosity

See Tests.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thuocngocanh.com/

You are viewing the BP 2023 (incorporating Ph.Eur. Supplement 11.2)

Guar Galactomannan

General Notices

(Ph. Eur. monograph 0908)

Action and use

Excipient.

Ph Eur

DEFINITION

Guar galactomannan is obtained from the seeds of *Cyamopsis tetragonolobus* (L.) Taub. by grinding of the endosperms and subsequent partial hydrolysis. The main components are polysaccharides composed of D-galactose and D-mannose at molar ratios of 1:1.4 to 1:2. The molecules consist of a linear main chain of β-(1→4)-glycosidically linked mannopyranoses and single α-(1→6)-glycosidically linked galactopyranoses.

CHARACTERS

Appearance

Yellowish-white powder.

Solubility

Soluble in cold water and in hot water, practically insoluble in organic solvents.

IDENTIFICATION

A. Mix 5 g of solution S (see Tests) with 0.5 mL of a 10 g/L solution of *disodium tetraborate R*. A gel forms within a short time.

B. Heat 20 g of solution S in a water-bath for 10 min. Allow to cool and adjust to the original mass with *water R*. The solution does not gel.

C. Thin-layer chromatography (*2.2.27*).

Test solution To 10 mg of the substance to be examined in a thick-walled centrifuge tube add 2 mL of a 230 g/L solution of *trifluoroacetic acid R*, shake vigorously to dissolve the forming gel, stopper the tube and heat the mixture at 120 °C for 1 h. Centrifuge the hydrolysate, transfer the clear supernatant carefully into a 50 mL flask, add 10 mL of *water R* and evaporate the solution to dryness under reduced pressure. Take up the residue in 10 mL of *water R* and evaporate again to dryness under reduced pressure. To the resulting clear film, which has no odour of acetic acid, add 0.1 mL of *water R* and 1 mL of *methanol R*. Centrifuge to separate the amorphous precipitate. Dilute the supernatant, if necessary, to 1 mL with *methanol R*.

Reference solution Dissolve 10 mg of *galactose R* and 10 mg of *mannose R* in 2 mL of *water R* and dilute to 10 mL with *methanol R*.

www.webofpharma.com

https://thuocngocanh.com/

Plate *TLC silica gel G plate R*.

Mobile phase *water R*, *acetonitrile R* (15:85 *V/V*).

Application 5 µL, as bands of 20 mm by 3 mm.

Development Over a path of 15 cm.

Detection Spray with *aminohippuric acid reagent R* and heat at 120 °C for 5 min.

Results The chromatogram obtained with the reference solution shows in the lower part 2 clearly separated brownish zones due to galactose and mannose in order of increasing R_F value; the chromatogram obtained with the test solution shows 2 zones due to galactose and mannose.

TESTS

Solution S

Moisten 1.0 g with 2 mL of *2-propanol R*. While stirring, dilute to 100 g with *water R* and stir until the substance is uniformly dispersed. Allow to stand for at least 1 h. If the apparent viscosity is below 200 mPa·s, use 3.0 g of substance instead of 1.0 g.

pH (*2.2.3*)

5.5 to 7.5 for solution S.

Apparent viscosity (*2.2.10*)

75 per cent to 140 per cent of the value stated on the label.

Moisten a quantity of the substance to be examined equivalent to 2.00 g of the dried substance with 2.5 mL of *2-propanol R* and, while stirring, dilute to 100.0 mL with *water R*. After 1 h, determine the viscosity at 20 °C using a rotating viscometer and a shear rate of 100 s^{-1}.

Insoluble matter

Maximum 7.0 per cent.

In a 250 mL flask disperse, while stirring, 1.50 g in a mixture of 1.6 mL of *sulfuric acid R* and 150 mL of *water R* and weigh. Immerse the flask in a water-bath and heat under a reflux condenser for 6 h. Adjust to the original mass with *water R*. Filter the hot solution through a tared, sintered-glass filter (160) (*2.1.2*). Rinse the filter with hot *water R* and dry at 100-105 °C. The residue weighs a maximum of 105 mg.

Protein

Maximum 5.0 per cent.

Carry out the determination of nitrogen by sulfuric acid digestion (*2.5.9*), using 0.400 g. Multiply the result by 6.25.

Tragacanth, sterculia gum, agar, alginates and carrageenan

www.webofpharma.com

https://thuocngocanh.com/

To a small amount of the substance to be examined add 0.2 mL of freshly prepared *ruthenium red solution R*. Examined under a microscope, none of the structures are red.

Loss on drying (*2.2.32*)

Maximum 15.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 5 h.

Total ash (*2.4.16*)

Maximum 1.8 per cent, determined on 1.00 g after wetting with 10 mL of *water R*.

Microbial contamination

TAMC: acceptance criterion 10^3 CFU/g (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU/g (*2.6.12*).

Absence of *Escherichia coli* (*2.6.13*).

Absence of *Salmonella* (*2.6.13*).

LABELLING

The label states the apparent viscosity in millipascal seconds for a 20 g/L solution.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristic may be relevant for guar galactomannan used as viscosity-increasing agent or binder.

Apparent viscosity

See Tests.

Ph Eur

© Crown Copyright 2022

www.webofpharma.com

https://thietbiuocngocanh.com/

Medicines & Healthcare products Regulatory Agency

tso
a Williams Lea company

Terms and conditions | Accessibility statement | Privacy policy | Cookie policy | Sitemap

www.webofpharma.com